Southwest
Oncology Group
A National Clinical Research Group

January 15, 2007

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

MEMORANDUM

Study Coordinator: Ian M. Thompson, Jr., M.D.
Phone number: 210/567-5643
E-mail: thompsoni@uthscsa.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The Southwest Oncology Group has withdrawn the SWOG-sponsored IND for finasteride effective January 12, 2006. The study referenced above is closed and all patients are off treatment.

FDA regulations require investigators to retain all research records, including patient charts, case report forms, endpoint assessments, IRB approvals, signed informed consent documents and all drug accountability records for at least two years after the IND has been withdrawn. Please retain records until at least **January 12, 2008**.

All supplies of finasteride for this study that remained at clinical sites after the end of the study should already have been returned according to protocol procedures. Please make sure that your drug accountability records adequately document this.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PCPT Statistical Center Staff - Susan Carlin
Ian M. Thompson, Jr., M.D.
ECOG - Jean MacDonald
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

June 30, 2004

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

STATUS NOTICE

Study Coordinator: Ian M. Thompson, Jr., M.D.
Phone number: 210/567-5643 E-mail: thompsoni@uthscsa.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure not built into study design

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE: EXTENDED FOLLOW-UP

The study referenced above will be permanently closed for the Extended Follow-Up study **effective 6/30/04.**

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Susan Carlin
Ian M. Thompson, Jr., M.D.
ECOG - Jean MacDonald
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

August 15, 2001

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

REVISION #1

Study Coordinator: Ian M. Thompson, Jr., M.D. Phone: 210/916-4417
E-mail: thompsoni@uthscsa.edu

IRB Review Requirements

( ) Full board review required

(√) Expedited review allowed

( ) No review required

REVISION #1

In response to a request for clarification on Amendment #11 from the Division of Cancer Prevention, the protocol referenced above has been revised as follows:

1. In order to clarify that the PSA and DRE procedures are recommended but not required, the bulleted items in Appendix 19.10, Section 3.0 have been revised and the Model Informed Consent Form in Section 19.10 has been revised under the first paragraph on page 103 to indicate that the annual visit "may (if you choose)" include PSA and DRE.

2. Other changes to the Model Informed Consent Form in Section 19.10. All of the listed changes are intended as clarification and may be added to the local consent form at the discretion of the responsible IRB.

   a. In order to clarify that the minimal follow up described in the Model Informed Consent Form applies to men who have a previous or current diagnosis of prostate cancer, the first paragraph on page 103 has been revised.

   b. A statement has been added to the first paragraph on page 103 to indicate that: "Whether you choose to take finasteride during the extended study is up to you (this is not part of the extended study)."

   c. A paragraph was added to page 103 to list potential reasons for removal of a participant from the extended study.

   d. A paragraph was added to page 104 to list alternatives to participation in the extended study.

e. A paragraph was added under "What are the Costs?" to clarify that the costs for the recommended DRE and/or PSA test will not be covered by this study. Study sites may choose to revise this statement to better describe the process within the site. Additionally, a sentence was added to indicate that: "Specifically, you or your insurance company will be charged for any prostate biopsy recommended as part of the extended study."

f. A "Fact Sheet" regarding PSA and DRE has been added as new page 107. This information may be helpful in the consent process and afterward.

3. A typographical error on the Study Calendar that occurred with Amendment #11 has been corrected. The "X1" symbol for "Anthropometric Measurements" in the "Extended Follow-Up" column was moved to indicate "DRE" instead. An "X" was added for "Participant Report - Sexual functioning" in the "Extended Follow-Up" column.

Determination of the need for participant re-consent and the manner of providing this information to participants is at the discretion of the local Institutional Review Board.

Replacement pages are enclosed for the face page and pages 27, 100 and 103 - 105. New page 107 has been added. Please insert them into your copy of the protocol.

This protocol remains permanently closed to new randomizations.

This memorandum serves to inform the NCI, Statistical Center, CALGB, NCCTG and ECOG.

cc: PCPT Statistical Center Staff - Deirdre Wehrman
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Alan R. Kristal, Dr.P.H.
William D. Figg, Ph.D.
Merck, Sharpe and Dohme - Elizabeth Stoner, M.D.
Oncology Therapeutics Network
Ellen Chase
ECOG - Jean MacDonald, Kerri Dolan
NCCTG - Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

January 5, 2001

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #11

Study Coordinator: Ian M. Thompson, Jr., M.D. Phone: 210/916-4417
E-mail: thompsoni@uthscsa.edu

IRB Review Requirements

(√) Full board review required
( ) Expedited review allowed
( ) No review required

AMENDMENT #11

The study referenced above has been amended as outlined below:

1. Procedures related to the "Extended Follow Up" for PCPT have been added as Appendix 19.10. The objectives of this effort are outlined in the appendix. This project requires additional informed consent from participants. A Model Informed Consent document for this effort is included in Appendix 19.10 and has been referenced in Section 18.0. The addition of this appendix is also referenced in Section 19.0. The Schema and Section 7.15 have been revised to reflect the addition of this appendix item.
2. A reference to the "Extended Follow-Up" and the WBC blood draw has been added to the Study Calendar.
3. Address information has been updated for Drs. Thompson, Brawer and Crawford on the face page.
4. The Guidelines for Reporting of Adverse Events in Section 16.0 have been updated to include Specific Adverse Event Reporting Guidelines for PCPT End-of-Study Prostate Biopsies. The following sentences were added to Section 7.7c as a reminder: "Good Medical Practice guidelines should be observed at the time of the end-of-study prostate biopsy. Medications that interfere with normal coagulation should be discontinued for an appropriate period of time prior to prostate biopsy."
5. The Participating Study Centers list in Appendix 19.6 has been updated to reflect current participating Study Centers and their names.

Replacement pages are enclosed for the face page and pages 3, 24, 26, 27, 36, 41, 46 and 65 - 69. Pages 98 - 106 have been added as the new Appendix 19.10. Please insert them into your copy of the protocol.

This protocol remains permanently closed to new randomizations.

This memorandum serves to inform the NCI, Statistical Center, CALGB, NCCTG and ECOG.

cc: PCPT Statistical Center Staff - Deirdre Wehrman
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Alan R. Kristal, Dr.P.H.
William D. Figg, Ph.D.
Merck, Sharpe and Dohme - Elizabeth Stoner, M.D.
Oncology Therapeutics Network
Ellen Chase
ECOG - Jean MacDonald, Kerri Dolan
NCCTG - Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

December 10, 1999

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #10

Study Coordinator: Ian M. Thompson, Jr., M.D. Phone: 210/916-4417
E-mail: thompsoni@uthscsa.edu

AMENDMENT #10

The study referenced above has been amended as outlined below:

1. Procedures for collecting white blood cells and plasma have been added as Appendix 19.9. The objectives of this effort are outlined in the appendix. This project requires additional informed consent from participants. A Model Informed Consent document for this effort is included in Appendix 19.9 and has been referenced in Section 18.0. The addition of this appendix is also referenced in Section 19.0.

2. The ADR reporting guidelines in Section 16.0 have been amended to clarify that: "New diagnoses of cancer, including prostate cancer, in PCPT participants need not be reported as adverse events. However, all diagnosis of cancer must be reported as assessment data in accordance with Section 9.0 and the Study Manual."

3. The Participating Study Centers list in Appendix 19.6 has been updated to reflect current participating institutions and names.

4. Editorial errors were corrected on page 41 (change of date in upper right corner from "2/25/99" to "3/2/99") and page 45a (addition of "Appended 3/2/99" in upper right corner).

Replacement pages are enclosed for pages 36, 41, 45a, 46 and 65 - 69. Pages 91 - 97 have been added as the new Appendix 19.9. Please insert them into your copy of the protocol.

An update to the PCPT Study Manual that includes detailed procedures for blood collection, processing and shipment and the required forms will be distributed by the Statistical Center in January 2000.

This protocol remains permanently closed.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Jeffrey Smith
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Alan R. Kristal, Dr.P.H.
William D. Figg, Ph.D.
Merck, Sharpe and Dohme - Elizabeth Stoner, M.D.
Oncology Therapeutics Network - Fadia Alaraj
Ellen Chase
ECOG - Jean MacDonald, Kerri Dolan
NCCTG - Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

March 2, 1999

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #9

In order to support retention and adherence to the study referenced above, a central database of participant mailing addresses will be established at the Southwest Oncology Group Statistical Center. This PCPT Participant Database allows for direct distribution of study-related information to participants.

For specific information and instruction for implementing the Participant Database, please refer to Appendix J of the PCPT Study Manual.

This project requires additional informed consent from participants agreeing that their addresses may be sent to the Statistical Center. Section 18.0 of the study referenced above has been amended to insert the Model Informed Consent document for the Participant Database. Page 41 has been amended and a new page 45a has been added to prevent extensive repagination. Please insert them into your copy of the protocol.

This protocol remains permanently closed.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Jeffrey Smith
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Alan R. Kristal, Dr.P.H.
William D. Figg, Ph.D.
Merck, Sharpe and Dohme - Elizabeth Stoner, M.D.
Oncology Therapeutics Network - Fadia Alaraj
ECOG - Jean MacDonald, Kerri Dolan
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Operations Office
14980 Omicron Drive•San Antonio, TX 78245-3217•Telephone 210-677-8808•FAX 210-677-0006•http://www.swog.org

Southwest
Oncology Group
A National Clinical Research Group

September 9, 1998

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #8

The study referenced above has been amended as outlined below:

1. Dr. William Figg's "Cohort Study of CAG Repeat Length and Prostate Cancer" has been added as Appendix 19.8. Associated changes in the protocol body include the addition of Dr. Figg's address on page 2, the addition of Objective 1.9, the addition of background information on the cohort study of CAG repeat length on page 18 and the addition of a sentence in Section 11.14 covering Objective 1.9.

2. The phrase "biopsy proven" has been changed to "histologically proven" throughout the protocol to recognize that prostate cancer may be detected via TURP as an alternative to biopsy. The change is reflected in Sections 1.1, 10.0 (1st paragraph), 19.4 (1st paragraph) and Appendix 19.7 (Sections 3.1, 3.7 and 3.9). Additionally, several references to "biopsies" were changed throughout Section 11.0 to better reflect protocol intent.

3. Additionally, Elizabeth Stoner, M.D. has replaced Glenn Gormley, M.D., Ph.D. as the Mercke, Sharpe and Dohme contact person for this study. This change is reflected on page 2.

4. In Section 8.2 in the first sentence, the words "clinically acceptable" were added to describe symptoms for which patients should be requested to remain on study drug.

5. Finally, this study will not use the new NCI Common Toxicity Criteria version 2.X. This clarification is noted in Section 8.2 and 16.0 (ADR/AE Guidelines).

Replacement pages are enclosed for pages 2, 4, 18, 26, 28, 29, 31 - 33, 36, 58, 71 and 74 - 76. Pages 81 - 90 have been added as the new Appendix 19.8. Please insert them into your copy of the protocol.

This protocol remains permanently closed.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Jeffrey Smith
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Alan R. Kristal, Dr.P.H.
William D. Figg, Ph.D.
Merck, Sharpe and Dohme - Elizabeth Stoner, M.D.
Oncology Therapeutics Network - Fadia Alaraj
ECOG - Jean MacDonald, Kerri Dolan
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

December 15, 1997

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #7

The study referenced above has been amended as outlined below:

1. The contact information for Drs. Miller, Natale and the Statistical Center on pages 1 and 2 was updated. Additionally, Dr. Scott Lippman replaces Dr. Frank Meyskens as the Cancer Control Research Committee representative on this study.

2. A clarification was added to Section 7.6b (paragraph 6, last sentence) to the effect that the PSA prompt for a subsequent biopsy (after benign tissue is found on biopsy) will be an increase of 50% or more above **the PSA value that prompted the recommendation for the original biopsy**.

3. Section 7.7e has been amended to specify that only participants found to have **high grade** (Grade 2 - 3) PIN should undergo rebiopsy. Additionally, the section now also specifies that the rebiopsy must also use the sextant biopsy technique outlined in Section 7.7c.

4. Section 7.14e has been revised to be more consistent with the Study Manual. Section 7.14e.2 was updated to specify that patient will be removed from protocol treatment for initiation of treatment with finasteride "...or other 5-alpha reductase inhibitor." Additionally, Section 7.14e.6 was added to specify removal from protocol treatment for missed contacts.

5. Section 8.2 was amended to note that the approach outlined in this section (drug holiday) may be used for "...any symptom potentially due to the study drug."

6. Appendix Section 19.4 has been amended to provide the correct contact information for the Pathology Core Laboratory (page 60).

7. Appendix Section 19.6 has been amended to update Study Center information. The Sacramento Prostate Study Group has changed its name to Sutter Health Central. The Oklahoma CGOP Consortium Cancer Center of the Southwest has changed its name to Integris Troy and Dollie Smith Cancer Center. The Methodist Cancer Program in Indiana and Mercy Hospital in Pennsylvania are no longer listed as CCOPs. The Cancer Institute of New Jersey - Hamilton and the Cancer Program - St. Joseph Hospital have been added as new Study Centers.

Replacement pages are enclosed for pages 1, 2, 24 - 26, 60 and 65 - 69. Please insert them into your copy of the protocol.

This protocol remains permanently closed.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Oncology Therapeutics Network - Paul Purnell
ECOG - Jean MacDonald, Roger Tait
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

Faxed: May 7, 1997
Mailed: May 12, 1997

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

PERMANENT CLOSURE: RANDOMIZATION

The study referenced above will be permanently closed to randomization **effective 5/31/97.** All projected randomizations should have been completed by this date. Randomization closure has been approved by the Data and Safety Monitoring Committee and Steering Committee.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals -Jodie Baldwin
ECOG - Jean MacDonald, Roger Tait
NCCTG -Linda Knowlton
CALGB - Kathleen Karas

Southwest
Oncology Group
A National Clinical Research Group

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

December 30, 1996

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #6

The study referenced above has been amended as outlined below:

1. The contact information for Drs. Thompson, Miller, Crawford, Natale, Kristal, Gritz and Gormley on pages 1 and 2 was updated. Additionally, the Statistical Center address and telephone number were updated on page 2.

2. The possibility of gynecomastia/breast tenderness was added to Section 3.1b and to the side-effects section of the Model Informed Consent Form. Please inform your participants of this potential toxicity in the manner directed by your Institutional Review Board.

3. Section 7.6e was added to summarize off treament follow-up procedures. Refer to your Study Manual for more detailed instructions.

4. Paragraph 3 of Section II of the Model Informed Consent form has been amended to clarify the intent of the 3rd sentence. “Elevated” PSA levels would prompt the “recommendation” for biopsy, rather than “require” biopsy.

5. An editorial error was corrected in Appendix Section 19.2. The words “more than” were deleted from the description of T2a.

6. The telephone and FAX numbers of the Pathology Core Laboratory were updated in Appendix Section 19.4.

7. Appendix Section 19.6 was updated to include designation of all CCOP institutions and reflect changes for institutions which are no longer CCOPs. Additionally, Montana CCOP was added as a participating Study Center effective November 29, 1995.

Replacement pages are enclosed for pages 1, 2, 19, 24, 43, 44, 56, 60 and 65 - 69. Please insert them into your copy of the protocol. Additionally, a hard copy of the permanent closure notice is attached. Please attach it to the front of your copy of the protocol.

This protocol was permanently closed to new enrollment effective 12/6/96. A copy of the closure notice is attached.

This memorandum serves to inform the NCI, Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
Kathleen Karas - CALGB
Jean MacDonald - ECOG
Roger Tait - ECOG
Linda Knowleton - NCCTG

Southwest
Oncology Group
A National Clinical Research Group

Faxed: 10/25/96
Mailed: December 30, 1996

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

PERMANENT CLOSURE

The study referenced above will be permanently closed to enrollment **effective 12/6/96** as it has met its targeted accrual and closure has been approved by the Data and Safety Monitoring Committee.

Enrollments must be dated no later than 12/6/96 and faxed within one working day following the participant's enrollment. Randomizations will continue until at least April 1, 1997. Notification of the last acceptable date of randomization will follow.

This memorandum serves to inform the NCI and Statistical Center.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
ECOG - Jean MacDonald, Roger Tait, Linda Knowlton - NCCTG
CALGB - Kathleen Karas

Operations Office
14980 Omicron Drive· San Antonio, TX 78245-3217· Telephone 210-677-8808· FAX 210-677-0006

Southwest
Oncology Group
A National Clinical Research Group

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

February 5, 1996

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #5

The study referenced above has been amended as outlined below:

1. The contact information for Dr. Glenn Gormley of Merck, Sharpe and Dohme on page 2 was updated. Additionally, Joseph Unger was replaced by Laura Loll as secondary biostatistician.

2. By decision of the Data and Safety Monitoring Committee, a numerical PSA value will be reported on all participants with an "ELEVATED" PSA at annual examination. The reported PSA value for participants receiving placebo will be the measured value. The reported PSA value for participants receiving finasteride who are determined to be adherent to study drug will be adjusted by a factor calculated by the Statistical Center (with monitoring by the Data and Safety Monitoring Committee). Additionally, the decision was made to recommend PSA or DRE-prompted biopsy (rather than mandate it). These changes have been incorporated into Sections 2.0, 7.6a - b, 7.7, 7.10 and 19.5.

3. Section 7.6c was moved to Section 7.1 and Sections 7.6d and e were renumbered accordingly.

4. Section 7.11 and Appendix 19.4 were amended to clarify pathology procedures.

5. The Model Informed Consent Form has been amended as requested by the Data and Safety Monitoring Committee. Participants should be informed of this information as directed by your IRB.

   The seventh paragraph of Section I was amended to clarify the potential benefits of study participation.

   A section of the second paragraph of Section II was moved to create a new paragraph (now the fourth paragraph under Section II). This paragraph was also amended to indicate that biopsy may be recommended (rather than "will be recommended").

   A sentence was added to the end of the (now) sixth paragraph to help explain the purpose of monitoring participants for the risk of heart disease.

A phrase was added to the end of the third sentence of the (now) eighth paragraph of Section II to indicate that treatment of early prostate tumors which may be found during this study "... involves a significant risk of side-effects".

The final sentence of Section III was amended to delete the word "alternative".

6. The Hawaii Minority Based CCOP and the Greenville CCOP (South Carolina) have been added as participating Study Centers. This change is reflected in Section 19.6.

Replacement pages are enclosed for pages 2, 15, 16, 22 - 25 and 25a, 42 - 44, 59 - 62, 66 and 68. Please insert them into your copy of the protocol. Page 25a was added to prevent extenvise repagination.

This memorandum serves to inform the Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
ECOG
CALGB

July 1, 1995

To: PCPT Principal Investigators
PCPT Data Managers

From: Charles A. Coltman, Jr., M.D.
Chairman
Southwest Oncology Group

Re: ADR Reporting for PCPT

In response to several concerns which were expressed during the PCPT Workshop in Phoenix, I wish to clarify our requirements for the reporting Adverse Drug Reactions on SWOG-9217, Prostate Cancer Prevention Trial.

Because of the special nature of this study and the relatively long interval between participant contacts with the study sites, expectations of ADR reporting within 24 hours of the event may not be reasonable. Study Centers and Sites are expected to report any Grades 3-5 Unknown Reactions and Grades 4-5 Known Reactions to the Southwest Oncology Group's Operations Office **within 24 hours of being notified of the event**.

Personnel at the PCPT Study Sites should continue to encourage their participants to immediately report any side effects or medical problem to them. This should facilitate the reporting of adverse events in a more timely fashion.

A new Adverse Drug Reaction reporting form for PCPT is attached. PCPT data managers should use this new form immediately.

Participant I.D.: _____ **Initials**: _____

SWOG-9217: Prostate Cancer Prevention Trial
Adverse Drug Reaction Form

Institution Name/Affiliate: _____

Investigator: _____

Person Completing This Form: _____ Telephone #: _____

Enrollment Date: _____ Enrollment Drug ID: _____

Randomization Date: _____ Study Drug ID: _____

On Treatment: Yes _____ No _____ Date Off Treatment/Discontinued: _____

Toxicity Type: _____ Toxicity Grade of ADR: _____

Toxicity Category: Known ____ Unknown _____ Death _____ (choose one)

Toxicity Description:

Date ADR Started: _____ Date ADR Ended: _____

Date Site Infomred of Toxicity: _____ Date SWOG Called : _____

Pre-existing Conditions: pre- enrollment _____ pre-randomization: _____ (indicate all that apply)

_____

Signature of Investigator Date

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

April 14, 1995

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #4

The study referenced above has been amended as outlined below (additionally, Dr. Thompson's contact information was updated on the face page):

1. The Cardiovascular Assessments paragraph in Section 2.0 and Section 7.6 have been amended to better reflect the intent of the protocol regarding risk assessment.

2. Individuals previously diagnosed with Prostatic Intraepithelial Neoplasia (PIN) have been excluded from participation in this study. This is reflected in Section 5.6.

3. Section 6.1 has been amended to clarify that the factors outlined here are descriptive factors rather than stratification factors. Also, the age descriptive categories have been changed.

4. The Model Informed Consent Form has been amended as requested by the Data and Safety Monitoring Committee. Participants should be informed of this information as directed by your IRB.

   The third paragraph of Section I has been replaced with three new paragraphs outlining storage of serum and tissue samples, and their possible use in future studies. The sixth paragraph of Section II has been amended to clarify that participants are "expected to" continue on the study for seven years. Section VII has been amended to soften the tone of Sentence 3 and indicate that access to medical records is voluntary. Section X has been amended to delete the last phrase of the second sentence. Finally, a box was added to the bottom of the form for participants to check if they do not wish to be contacted for future studies.

Replacement pages are enclosed for pages 18, 21, 22, 23, 42, 43 and 45 and should be inserted into your copy of the protocol.

This memorandum serves to inform the Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
ECOG
CALGB

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

February 3, 1995

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #3

The study referenced above has been amended as outlined below:

1. Dr. Alan Kristal's "Diet Ancillary Study" has been added as Appendix 19.7. Associated changes in the protocol body include the addition of Dr. Kristal's address on page 2, the addition of Objective 1.8, the addition of background information on the dietary assessment on page 18, mention of the dietary assessment in Section 7.6, the addition of Section 7.6e, the addition of the "Food Frequency Questionnaire" and anthropometric measurements to the Study Calendar (Section 9.0) and the addition of a sentence in Section 11.14 covering Objective 1.8.

2. Sections 8.2 and 16.0 (page 36) have been amended to clarify the regulatory requirements for the reporting of sexual side-effects in participants on this study. The alternative grading scales for Impotence, Loss of Libido and Ejaculate Volume provided in Section 8.2 are to be used only for eligibility purposes and routine reporting. They are not to be used for the determination of the need for an ADR report. The grading scales provided in the Southwest Oncology Group Toxicity Criteria (see Section 19.1) are to be used for the determination of the need for an ADR report. Additionally, the Southwest Oncology Group ADR form for reporting ADRs is enclosed for the use of PCPT institutions.

3. Phyllis Goodman, M.S. and Joseph M. Unger M.S. have been added as statisticians for this study, replacing Michael Wolf, M.S. This change is reflected on page 2.

4. A typographical error in the calculation of the PSA Index in the next to the last paragraph on page 15 was corrected.

5. Two of the risk-factors for CHD in Appendix 19.3 were deleted (cholesterol level and male gender) to be consistent with the algorithm for risk counselling. Also, a formula for calculating Ideal Body Weight was added.

6. The Pathology Review Procedures in Appendix 19.4 were updated.

7. The Colorado Cancer Research Program CCOP, the Louisiana State University CCOP in New Orleans, and the Main Line Health CCOP have been added as participating Study Centers. This change is reflected in Appendix 19.6.

Replacement pages are enclosed for pages 2, 4, 15, 18, 23, 24, 26, 27, 33, 36, 46, 57 - 61, 65, 66, 68 and the Southwest Oncology Group ADR Form. Pages 70 - 80 have been added as the new Appendix 19.7. Please insert them into your copies of the protocol.

This memorandum serves to inform the Statistical Center, CALGB and ECOG.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
ECOG
CALGB

Study Centers are responsible for transmitting all protocol communications to their affiliated Study Site(s).

August 10, 1994

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #2

The study referenced above has been amended as outlined below:

1. The possibility of hypersensitivity reaction with facial swelling and skin rash was added to Section 3.1b and to the side-effects section of the Model Informed Consent Form. Although this reaction has been seen in only a few patients and has generally been mild, please inform your participants of this potential toxicity.

2. Section 5.5 was amended to provide guidelines for potential participants with prostatitis and/or other clinical situations expected to raise the PSA value.

3. Section 5.22 has been amended to specify that the PSA assay for the final enrollment criteria is performed on the specimen drawn at the time of enrollment.

4. Section 7.5 was amended to include mention of interim telephone contact for follow-up.

5. Section 7.6c has been amended to change the criteria for referring participants for further evaluation for elevated cholesterol and other coronary risk factors and to correct editorial errors. Patients must be referred if: their Total Cholesterol is > 240; or Total Cholesterol is 200 - 240 and participant has had a definite prior myocardial infarction or myocardial ischemia such as angina pectoris; or Total Cholesterol is 200 - 240 and participant has ≥ 2 other risk factors (see Section 19.3).

6. Sections 7.7 and 7.9 have been amended to correct editorial errors.

7. Section 7.14f was added to provide a reference to the Study Manual for reactivation of participants.

8. The table in Section 11.11 has been corrected to reflect the proper power computations.

9. The Model Informed Consent Form (Section II) was amended to state: "You will not be informed which tablet you have been receiving until the end of the study, except in the case of a medical emergency." Additionally, the Model Informed Consent Form (Section II) was amended to clarify that the cholesterol screening test will be performed only for randomized participants.

10. Appendix Section 19.6 has been amended to include two new participating Study Centers, Mayo Clinic Scottsdale and Fairfax CCOP.

Replacement pages are enclosed for pages 19, 21 - 24, 26, 32, 43, 44, 44a, 65 and 69. Please insert them into your copies of the protocol.

This memorandum serves to inform the Statistical Center, ECOG and CALGB.

cc: PCPT Statistical Center Staff - Shannon Hill
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
Jack Geller, M.D.
Joseph Schmidt, M.D.
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
ECOG
CALGB

January 1, 1994

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

AMENDMENT #1

The study referenced above has been amended as follows:

1, John Crowley, Ph.D. was added to page 2 as an additional biostatistician for the study.

2. References to the Abbott IMx assay were removed from page 16, and Appendix 19.7 was deleted as we will be using the Hybritech assay rather than the Abbott IMx.

3. References to form numbers were added in Sections 3.1c and 5.19 for your convenience.

4. The phrase "within normal limits" in Section 5.4 was capitalized and placed in bold type for emphasis.

5. A reference to Section 7.6b was added to Section 5.5.

6. An exclusion for prior biologic therapy as treatment for cancer was added to Section 5.8.

7. The time frame for pre-enrollment physical examination was changed from 28 to 42 days.

8. Criteria for Final Enrollment based on toxicity assessment (Section 5.23) were changed to compensate for participants who may already be experiencing symptoms of impotence, loss of libido and changes in ejaculate volume before beginning treatment. Supplementary Toxicity Criteria were added in Section 8.2 to help better assess these toxicities.

9. Editorial errors were corrected in Sections 7.2, 7.3, 7.6b and the Model Informed Consent Form.

10. A "NOTE" was added to Section 10.3 to clarify Performance Status grading for a participant with a permanent disability.

11. Two sentences were added to Section III of the Model Informed Consent Form to ask participants to refrain from donating blood or blood products while being treated on this study.

Replacement pages are enclosed for pages 2, 16, 20 - 23, 26, 28, 43, 44 and 46. Please insert them into your copy of the protocol. Please remove page 70 from your copy of the protocol.

This memorandum serves to inform the Statistical Center, ECOG and CALGB.

cc: PCPT Statistical Center Staff - Katie White
Ian M. Thompson, Jr., M.D.
Gary Miller, M.D.
ECOG
CALGB
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson

October 1, 1993

Effective date: October 13, 1993

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

ACTIVATION AMENDMENT

THE STUDY REFERENCED ABOVE WILL BE ACTIVE FOR PARTICIPANT ACCRUAL EFFECTIVE OCTOBER 13, 1993. DO NOT ATTEMPT TO ENROLL ANY PARTICIPANTS BEFORE THAT DATE.

Between the July 12, 1993 draft of the protocol referenced above and activation, the following editorial revisions have been made:

1. Dr. Ian Thompson's phone number has been updated, Michael Wolf, M.S. replaces Dr. Blumenstein as study biostatistician and Dr. Ellen Gritz's address has been updated on the face page.

2. In Background (Section 2.0, page 15) a section regarding "PSA Index" has been added and corresponding reference numbers 51 through 54 have been added to the Bibliography.. Additionally, Appendix Section 19.7 was added to provide information on quality control procedures for the PSA assay used in this study. Accordingly, Table 1, the PSA Index Flow Chart for placebo recipients and Table 2, the PSA Index Flow Chart for finasteride recipients have been deleted.

3. The wording of contraceptive use was changed in Section 5.16. As self-administered forms will be provided in both Spanish and English, the requirement in Section 5.19 has been changed to specify that participants who understand English or Spanish may complete these forms. The collection of Quality of Life information has been added to the First Visit eligibility requirements. A new Section 5.21 has been added to state a time frame for prestudy tests.

4. Section 7.6b - a description of other causes for increased PSA and subsequent PSA test postponement has been added to the end of the ection. Section 7.7a - The time frame for PSA or DRE prompted TRUS and biopsy has been added. Section 7.7e - has been added to include course of action if Prostatic Intraepithelial Neoplasia (PIN) is found in participants.

5. In the Consent Form, a sentence was added to explain that all participants in the study will receive placebo at some point during their participation. The wording of the section regarding birth

regulation during the study has been changed. Section V, Sentences have been added to account for possibility of errant fax transmission of medical records.

6. Appendix Section 19.2 was updated with the current TNM staging.

7. Facsimile and telephone numbers for the Core Laboratory were added to Appendix Section 19.4.

8. In Appendix Section 19.6, the participation institutions were updated with their current preferred names.

Editorial and format changes have also been made throughout the protocol. Enclosed please find complete copies of the study for your institution. Please replace any previous copies with the version dated October 13, 1993.

cc: PCPT Statistical Center Staff - Katie White
Ian M. Thompson, Jr., M.D.
ECOG
CALGB
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson
Gina Atwood

July 12, 1992

TO: Participating Study Centers listed in Appendix 19.6

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-9217**, "Chemoprevention of Prostate Cancer with Finasteride (Proscar®), Phase III, Intergroup." Study Coordinators: Drs. I. Thompson, M. Brawer, G. Miller, E. D. Crawford, et al.

MEMORANDUM

The study referenced above is being distributed to you at this time strictly to allow time for IRB review prior to its official activation.

This study is not currently active, and is not open for participant registration or treatment.

The institutions listed here are the designated Study Centers for the PCPT. Each of these Study Centers may have affiliated Study Site(s) which will also be participating in the study. The Study Center, however, serves as the administrative and communications center. The Study Center is responsible for transmitting communications and administrative needs to its affiliated Study Site(s).

Study Centers are also responsible for transmitting copies of all protocol communications to their affiliated Study Site(s). Three copies of the protocol are sent to you at this time. Please contact me (Dana Sparks) at the Southwest Oncology Group Operations Office if you need more or fewer copies of protocol mailings.

This memorandum serves to inform the Statistical Center.

cc: PCPT Statistical Center Staff - Katie White
Ian M. Thompson, Jr., M.D.
ECOG
CALGB
Merck, Sharpe and Dohme - Glenn J. Gormley, M.D., Ph.D.
Axion Pharmaceuticals - Dan Paterson

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY
Amended 4/14/95
Amended 12/30/96
Amended 12/15/97

SWOG-9217
PCPT
IRB Submission July 12, 1993
Activated October 13, 1993
Amended January 5, 2001

SOUTHWEST ONCOLOGY GROUP

CHEMOPREVENTION OF PROSTATE CANCER WITH FINASTERIDE (PROSCAR)

PHASE III

PARTICIPANTS: See Appendix Section 19.6

STUDY COORDINATORS:

Ian M. Thompson, Jr., M.D. (Urological Oncology)
UTHSCSA - Division of Urology
7703 Floyd Curl Drive
MSC 7845
San Antonio, TX 78284-7845
Phone: 210/567-5643
Fax: 210/567-6868

Michael K. Brawer, M.D. (Urological Oncology)
Northwest Prostate Inst
1560 N 115th St
Suite 209
Seattle, WA 98133
Phone: 206/368-6599
Fax: 206/368-1191

Gary J. Miller, M.D., Ph.D. (Pathology)
University of Colorado
Division of Pathology, Box B216
4200 East 9th Avenue
Denver, CO 80262-0216
Phone: 303/315-5408
Fax: 303/315-6761

AGENTS:

Finasteride (Proscar) (IND-28422)

E. David Crawford, M.D.
(Genitourinary Committee Chair-Urological Oncology)
University of Colorado
Division of Urology, Box C-324
4200 East 9th Avenue
Denver, CO 80262-0001
Phone: 303/315-5936
Fax: 303/315-0662

mb

(Protocol Last Changed 8/15/01)

STUDY COORDINATORS (contd.)

Ronald B. Natale, M.D. (Medical Oncology)
c/o Deirdre Fischer, RN
Cedars-Sinai Medical Center
Becker Building, Suite 213
8700 Beverly Blvd
Los Angeles, CA 90048
Phone: 310/967-1101
Fax: 310/652-8759

Phyllis Goodman, M.S. (Biostatistician)
John Crowley, Ph.D.
Laura Lovato, M.S.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-651
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-6868
Fax: 206/667-6869

Ellen Ruth Gritz, Ph.D.
Department of Behavioral Science
Box 243
MD Anderson Cancer Center
The University of Texas
1515 Holcombe Boulevard
Houston, Texas 77030
Phone: 713/745-3187
Fax: 713/794-4730

Scott M. Lippman, M.D.
(Cancer Control Committee Chair-Medical Oncology)
MD Anderson Cancer Center
Department of Clinical Cancer Prevention
Room HMB 3.060, Box 236
1515 Holcombe Blvd
Houston, TX 77030-4009
Phone: 713/745-3658
Fax: 713/745-4230

Carol M. Moinpour, Ph.D. (Quality of Life)
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-557
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
Fax: 206/667-4408

Alan R. Kristal, Dr.P.H. (Diet Ancillary Study)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-702
Seattle, WA 98109-1024
Phone: 206/667-4686
Fax: 206/667-5977

William D. Figg, Ph.D. (CAG Repeat Study)
Clinical Pharmacokinetics Unit, Dev. Thera. Unit
National Cancer Institute
9000 Rockville Pike
Bldg. 10, Room 5A901
Bethesda, DM 20892
Phone: 301/402-3622
Fax: 301/402-8606

ECOG STUDY COORDINATORS:

David G. McLeod, M.D. (Urological Oncology)
Chief of Urology
Walter Reed Army Medical Center
6825 16th Street, NW
Washington, D.C. 20307

Patrick J. Loehrer, M.D. (Medical Oncology)
Indiana University Medical Center
Room A109
926 W. Michigan St.
Indianapolis, IN 46223

CALGB STUDY COORDINATORS:

Gerald L. Andriole, M.D. (Urological Oncology)
Jewish Hospital at
Washington University School of Medicine
216 S. Kingshighway
St. Louis, MO 63110

Nicholas J. Vogelzang, M.D. (Medical Oncology)
University Of Chicago Medical Center
5841 S. Maryland Ave., Box 420
Chicago, IL 60637-1470

Vincent Vinciguerra, M.D. (Cancer Control)
North Shore University Hospital
Division of Oncology
300 Community Drive
Manhasset, NY 11030

MERCK, SHARPE AND DOHME CONTACT PERSON:

Elizabeth Stoner, M.D., Vice President
Endocrinology & Metabolism
Merck Research Laboratories
Merck & Co., Inc.
P.O. Box 2000, RY33-524
Rahway NJ 07065-0900
Phone: 732 594 5095
Fax: 732 594 8170

PLEASE REFER ANY MEDICAL QUESTIONS TO THE
SOUTHWEST ONCOLOGY GROUP STUDY COORDINATORS

SCHEMA

Men ages ≥ 55 with no prior history of prostate cancer
with normal Digital Rectal Examination (DRE)
PSA to be performed at a Central Laboratory Facility (CLF)

↓

Enrollment (Registration)

↓

3 month
Enrollment Period

Final Enrollment (Randomization)

↓ Placebo

↓ Finasteride

Follow-up q 3 months by telephone contact and/or
clinic visit as noted on the Study Calendar

↓

Annual DRE and PSA
(Prostate biopsy if abnormal DRE or elevated PSA)

↓

For each participant, prostate biopsy at seven year anniversary following Final Enrollment.

↓

Follow-up off-treatment as required per Appendix Section 19.10

1.0 OBJECTIVES

Primary Objective

1.1 To test the difference in the histologically-proven prevalence of carcinoma of the prostate between a group of participants treated with finasteride and a group treated with placebo for seven years.

Secondary Objectives

1.2 To assess the effect of finasteride on the stage and grade of carcinoma of the prostate at the time of diagnosis.
1.3 To assess the toxicity and side effects of finasteride when administered on a long-term basis.
1.4 To estimate the difference in the total and prostate-cancer specific mortality between men treated with finasteride and those treated with placebo.
1.5 To estimate the difference in incidence and severity of benign prostatic hyperplasia between men treated with finasteride and those treated with placebo.
1.6 To estimate the sensitivity, specificity and predictive values of digital rectal examination (DRE), PSA (Prostate Specific Antigen) and PSA + DRE as screening tests for the detection of prostate cancer, and to estimate the effect of long-term finasteride treatment on these screening parameters.
1.7 To assess the effect of long-term treatment with finasteride on the participants' self-report of urinary and sexual function symptoms and other Quality of Life dimensions.
1.8 To investigate whether dietary fat, assessed as intake of total fat, saturated fat and high fat foods, is associated with increased risk of prostate cancer (see Appendix 19.7 for related aims).
1.9 To assess the degree to which CAG trinucleotide repeat length is associated with an increased risk of prostate cancer (see Appendix 19.8 for related aims).

2.0 BACKGROUND

This is a chemoprevention trial of finasteride to reduce the incidence of prostate cancer in healthy men.

Prostate cancer is now the most common tumor in U.S. men with an estimated 132,000 new cases diagnosed in 1992 and approximately 34,000 deaths during this year. *(1)* It has been estimated that of Caucasian and African-American males born in 1985, 8.7% and 9.4%, respectively, will be diagnosed with carcinoma of the prostate and that 2.6% and 4.3% will die from the disease. *(2)*

With the dramatic increase in the number of cases of the disease and the steady increase in mortality, emphasis has been placed on improving early diagnosis to attempt to treat the disease at an earlier, and potentially more curable stage. Despite intensive efforts in this realm, in patients aggressively screened for the disease over half are found to have disease beyond the confines of the prostate at the time of surgical excision and many of these patients will be expected to fail treatment if followed for sufficient time. *(3)* Additionally, there is no evidence that current early detection efforts have had or will have any impact upon the morbidity or mortality from carcinoma of the prostate. *(4)*

An ideal method to reduce the mortality and morbidity of carcinoma of the prostate is through primary prevention: either through a reduction in the number of clinically-evident cases or through a reduced age-dependent rate of development of the disease such that the disease would become evident 5, 10, or 15 years later than otherwise occurs. Although there is evidence that the development of this tumor may be related to dietary habits, problems in changing such patterns of behavior and the need for life-long intervention make such a preventative method difficult in practice. *(5)*

Chemoprevention of prostate cancer is an attractive alternative and there are various agents which, through several different mechanisms, may be useful for this application. A group of compounds termed retinoids have been demonstrated to control differentiation and proliferation of various cell lines. Epidemiologic trials concerning the effect of dietary vitamin A have been inconclusive but in Lobund-Wistar rats with prostate adenocarcinoma-III cells who were treated with 4-hydroxyphenol retinamide (4-HPR), metastatic disease was significantly reduced. *(6-8)* Unfortunately, several types of side effects have been encountered with this agent, most notably, dark adaptation and skin toxicities. *(9)* In animal studies, chronic feeding of 4-HPR has been noted to cause body weight reduction and reduction in food intake as well as hepatomegaly and an increase in SGPT, serum cholesterol, and triglyceride levels. In a study of chemoprevention of prostate cancer in asymptomatic men who must take a pharmaceutical for a prolonged period of time (often in excess of 10 years), even minimal degrees of toxicity would probably lead to significant compliance problems and confound interpretation of results.

One attractive agent for the prevention of carcinoma of the prostate has been suggested by the study of an inherited form of intersex. In this small group of patients, an inherited deficiency in 5-alpha reductase, the enzyme which catalyzes the conversion of testosterone to dihydrotestosterone (DHT), leads to a form of male pseudohermaphroditism characterized by mild external genitalia anomalies at birth. *(10,11)* These males virilize at puberty but have minimal facial hair, no temporal hair loss, no acne, and have an underdeveloped prostate. The development of benign prostatic hyperplasia and carcinoma of the prostate in these individuals has not been reported. Recently, finasteride (Proscar) a 4-azasteroid competitive inhibitor of human 5-alpha reductase has been synthesized. This agent causes a profound reduction in circulating and cellular dihydrotestosterone, similar to the findings with the inherited enzyme deficiency.

In addition to the evidence from the inherited deficiency of 5-alpha reductase that finasteride may be useful for the chemoprevention of prostate cancer, there is additional evidence supporting the importance of the role of DHT in the initiation and progression of the disease. These data can be summarized as follows:

1. Although data are conflicting, some studies have suggested that men with relatively-lower serum androgen levels have a decreased risk of developing carcinoma of the prostate. *(12)*

2. Analysis of human prostate cancer tissues have demonstrated that the DHT/DNA ratio is higher in more differentiated tumors. *(13,14)* If such is the case, a reduction of intraprostatic DHT may reduce its ability to serve as a promoter of the development of prostate cancer.

3. Although a recent trial in patients with metastatic carcinoma of the prostate was disappointing (in terms of percent decrease or normalization of PSA), studies have demonstrated that inhibition of 5-alpha reductase can reduce progression of prostate cancer. *(15,16)*

4. There are ample data demonstrating the dramatically-increased risk of prostate cancer (both incidence and mortality) among U.S. African-Americans and the significantly-less risk among Asian countries, especially China and Japan. *(17,18)* The significantly-increased risk of disease among U.S. African-Americans has been postulated to be related to the relative increase in circulating testosterone in this group, estimated to be 10 - 15% higher than in U.S. Caucasians. *(12)* Ross, et al, recently conducted a study of U.S. Caucasians and African-Americans as well as rural Japanese men to determine whether variations in 5-alpha reductase activity among these populations could explain the variability in prostate cancer risk. *(19)* In a group of 50 U.S. Caucasians, 50 U.S. African-Americans, and 54 Japanese young men, testosterone, sex hormone binding-globulin binding capacity (SHBG), as well as levels of 3-alpha, 17-beta androstanediol glucuronide (a-diol-g) and androsterone glucuronide (A-g) (indirect measures of 5-alpha reductase activity in serum) were measured. As previously published, African-Americans

had an 11% higher serum testosterone as well as a 9% higher SHBG level. Significantly-higher levels of A-diol-g and A-g were detected in U.S. African-Americans and Caucasians than in Japanese men. These data suggest that reduced 5-alpha reductase activity may play a protective role in the development of prostate cancer in Japanese men.

5. Five-alpha reductase inhibition with finasteride causes a dose-dependent inhibition of two human prostate cancer cell lines, in vitro. *(20)* In the latter study, the 5-alpha reductase inhibitor used was finasteride, the agent to be used in this study.

Pre-clinical Safety Profile

The potential toxicity of finasteride has been extensively studied in vitro and in vivo. In acute toxicity studies, the oral LD_{50} values in mice, rats and dogs ranged from 300 to 1000 mg/kg, which corresponds to 3000 to 10,000 times the human dose. Doses up to 8000 times the therapeutic dose have been tested in 3 month studies. In addition, finasteride has been tested in a battery of genetic toxicity studies and carcinogenicity studies in rats and mice. Biochemical mechanisms underlying specific finasteride-related changes have been studied in detail. These studies have demonstrated that finasteride has a low order of toxicity. Finasteride was tested in five different genetic toxicity assays to evaluate mutagenic potential with no evidence of drug induced DNA damage, chromosomal aberration or tumorigenicity at relevant concentrations of the drug. The only drug-related tumor observed was Leydig cell adenoma in male mice treated with 250 mg/kg/day.

Evaluation of the developmental toxicity of finasteride in rats has demonstrated that in utero exposure to the drug leads to some developmental abnormalities only in males (such as hypospadias). These effects were observed at low doses and are expected pharmacological effects of the drug due to 5-alpha reductase inhibition and have no direct implication for the intended patient population.

Reproductive studies in male rats and rabbits were conducted to evaluate the potential toxicity of finasteride on various male reproductive parameters. Finasteride had no significant effects on either the semen parameters or on fertility in male rabbits. Detailed studies have demonstrated that the drug has no effect on spermatogenesis, mating behavior, or on fertilizing capacity of the sperm. Decreased fertility in finasteride-treated male rats is rapidly reversible and caused by a species-specific effect on seminal plug formation (essential for normal fertility only in rats) but not relevant to men.

Thus, the wide safety margin in animal studies and the relevance of these findings to the intended patient population support the use of finasteride in man for the intended clinical study.

Clinical Safety Profile

In the North American Phase III BPH Trial, 297 men received 5 mg qd of finasteride. Two hundred ninety-eight men received 1 mg qd of finasteride and 300 men received placebo once daily for 12 months. *(21)* Finasteride was well tolerated in this study with less than 2% of men withdrawing from the study due to drug related events. The drug related symptoms which occurred in at least one-half a percent or more of men are shown in Figure 1 for the 5 mg and placebo treated patients. The overall frequency of these symptoms were similar in the finasteride and placebo groups. Only the proportion of men reporting decreased libido and decreased ejaculate volume were significantly higher in the finasteride group. *(21)*

Two deaths occurred during the 12 month trial (both on 1 mg of finasteride) and four men were diagnosed with prostate cancer (1 on placebo, 2 on 1 mg and 1 on 5 mg finasteride). Three of four men diagnosed with prostate cancer had baseline pre-study PSA levels greater than 10 ng/ml. There were no significant effects on vital signs, visual acuity or laboratory tests. These patients have recently completed two years of continuous therapy for benign prostatic hyperplasia (BPH) which has confirmed the safety profile.

In a separate study (AUA Abstract, 1992), no effect on semen production (sperm count, motility or morphology) was seen in normal volunteers. The only observed effect was a median reduction in ejaculate volume of 1/2 cc which was reversible.

In summary, finasteride appears to have very limited toxicity in animal and human studies. The only consistent observation with clinical relevance are the effects on the developing male fetus and the small number of men reporting changes in their libido. The safety profile of finasteride, therefore, supports the chemoprevention trial.

FIGURE 1

SIDE EFFECT	5 MG FINASTERIDE	PLACEBO
Digestive System		
Abdominal pain	1.0	0.3
Flatulence	1.0	0.7
Nausea	0.7	1.0
Nervous System		
Dizziness	0	0.7
Headache	0.7	0.7
Decreased Libido	4.7*	1.3
Urogenital System		
Breast Pain	0.3	0
Dysuria	0.7	0
Ejaculatory Disorder	4.4*	1.7
Impotence	3.4	1.7
Orgasm Dysfunction	0.7	0.3
Testicular Pain	1.0	0.7
Eye		
Lens Change	0.7	0
Lens Opacities	0	0.7
Miscellaneous		
Rash	0.7	0.3
Asthenia	1.0	1.0
Pelvic Pain	0.3	0.7

* $P < 0.05$ vs. placebo

The composite of this information suggests the following:

1. The development of carcinoma of the prostate is profoundly influenced by the androgenic milieu of the male individual.

2. Inherited deficiency of 5-alpha reductase effectively prevents development of the prostate and thereby prevents the development of diseases of this gland.

3. The risk of the development of carcinoma of the prostate in various populations may be directly-related to the relative levels of 5-alpha reductase.

4. The 5-alpha reductase inhibitor, finasteride, has a very low risk of side effects and patient compliance with this agent with prolonged administration should be excellent.

5. Finasteride inhibits growth of prostate cancer cells *in vitro*.

These five observations provide support for the conduct of an investigation of the chemopreventive effect of finasteride on carcinoma of the prostate. This study will be a Phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy of finasteride in the prevention of carcinoma of the prostate.

STUDY DESIGN CONSIDERATIONS

The principal difficulty with a trial comparing finasteride and placebo in the development of carcinoma of the prostate is that the study drug may influence detection of prostate cancer. Finasteride, in the doses used in this study, has been demonstrated to reduce serum PSA, a principal method of prostate cancer detection, by approximately 50%. Thus, if PSA is employed as a method of identifying those participants who may have developed prostate cancer since study entry, more participants receiving placebo would undergo prostate biopsy. Due to the direct relationship between the rate of prostate biopsy and the detection rate of prostate cancer, the disease detection rate in the placebo arm would be artificially-increased.

Due to the unique problem of any study which assesses the ability of an agent to prevent carcinoma of the prostate (i.e., that one test for the detection of prostate cancer is affected by the agent itself, thus confounding the detection rate), several study designs were considered. It is important to review these options as the issues considered in various study designs influenced the development of the final study design.

STUDY DESIGN #1. BLINDED PSA.

Perhaps the most practical design for a chemoprevention trial in which the agent affects PSA is one in which the value of PSA is blinded to investigator and participant. By doing so, the pattern of change of PSA could be assessed retrospectively to determine disease-predictive values after study closure. However, such a trial (1) has potential bias and (2) would not be acceptable to a population of healthy men. The latter problem, acceptability, was evident at several meetings of investigators who are actively studying large groups of healthy men and patients with prostate cancer. The consensus was that men are acutely interested in the PSA value and that to deny them this knowledge would either (1) be unacceptable, thus hampering accrual to the study or (2) lead many participants to obtain PSA values outside the study, potentially unblinding the study and leading to a differential biopsy rate in the two treatment groups.

The second problem, "DRE Bias", would be introduced by the unknown, yet potential effect of finasteride on digital rectal examination (DRE). It is known that finasteride leads to a reduction in volume of the prostate - approximately 20% over six months. Much of the reduction is probably due to a decrease in the volume of adenomatous tissue. This decrease in gland volume could lead to either an overdetection or underdetection bias, based upon DRE alone. If a reduction in the gland volume causes a more homogenous-feeling prostate, participants treated with

finasteride may have a lower number of prostate biopsies. If the drug causes no change in the development of prostate cancer this decreased rate of biopsy in the finasteride arm may detect a lower rate of disease unrelated to the true incidence of cancer. Conversely, if finasteride leads to a reduction in volume of the gland, enhancing subtle palpable abnormalities within the prostate, a higher biopsy rate may result, again leading to an increased detection rate which may have no correlation with the true incidence of the disease. The degree of "DRE Bias" which is operational should be small as there appears to have been similar prostate cancer detection rates in both arms of the Phase III BPH trials. *(21)*

Due to a consensus that a blinded PSA study would be unacceptable to participants, this study design was abandoned.

STUDY DESIGN #2. INDEXED PSA.

Recognizing that a study in which PSA results are blinded would be unacceptable to participants, a system in which PSA was indexed or adjusted was investigated. As PSA can potentially cause significant detection bias in a placebo study arm, and as there is a significant body of information relating to the impact of finasteride upon PSA, an attempt was made to design a system by which an equal opportunity for detection of prostate cancer exists in both arms of a Phase III trial of finasteride for chemoprevention.

The first such system was based upon a primary study objective of a reduction in the incidence rate of carcinoma of the prostate. To help assure equal diagnostic surveillance in both arms of the study, a monitoring system was sought which was designed to make the expected number of participants undergoing diagnostic tests for prostate cancer the same in both the treatment group and in the placebo group. This would require having different definitions of an "abnormal" PSA in the two groups. This system would then create equal opportunity for prostate cancer detection by having equal numbers of men undergoing biopsies in the two groups. Conversely, such a study design would not attempt to create equal numbers of cancers detected in the two groups as doing so would force equality of the numbers of primary endpoints in the two groups, invalidating the trial by forcing the study to the null hypothesis. Thus, the fundamental basis for this study design is to provide equal opportunity for PSA-driven detection of prostate cancer.

Data relative to the operational characteristics of PSA in healthy individuals and those receiving finasteride over a prolonged period of time are unavailable. However, these data are available in longitudinal studies of individuals undergoing screening for carcinoma of the prostate and in patients with BPH who are receiving finasteride. In order to validate these data in a group of healthy individuals, the study design would require a smaller segment of the study population who would enter the protocol a year prior to the main body of the study population. This initial group of participants is hereafter referred to as the Vanguard Group.

This study design would randomize men with a normal DRE and a normal PSA to finasteride or placebo. Subsequent PSA and DRE examinations would be performed at months six and twelve and annually thereafter. A criterion in each group would be established from current data as an abnormal value (above which further evaluation for the presence of prostate cancer would be conducted). (This could be an absolute value of PSA, an annual rate of change, the percent change of PSA above baseline, etc.) The second monitoring characteristic which would be selected would be the positive predictive value (PPV) of a PSA that exceeds the criterion. To recall statistics, %PPV = (% Prevalence) * (Sensitivity) / (% Yield) where % Yield is the percent of men who exceed the criterion.

To complete these decisions, several sources of data are available. For sensitivity, data are available from screening trials at the University of Washington as well as from Washington University in St. Louis. *(3,22)* An additional source is the Baltimore Longitudinal Study of Aging (BLSA). *(23)*

For the % Yield calculations, data are also available from several sources. One source is the serial PSA measurements in the placebo group of the North American Phase III clinical trials of

finasteride, limiting the population to the men in the placebo group whose baseline PSA was less than 4.0 ng/ml.

Prevalence in the above calculations refers to the percent of men in the study population in whom prostate cancer will be diagnosed over a given interval of time. Two reasonable intervals would be (1) the initial one-year period after baseline and (2) the total trial duration. The reason for making a separate calculation for the one-year period after baseline is that it would incorporate the results of the monitoring after one year based upon a Vanguard Group and will allow confirmation of estimates of the above assumptions.

Estimates of disease prevalence are difficult, as in very few studies are all men who are tested subsequently subjected to biopsy for confirmation. In Cooner's series of men undergoing screening evaluations, of those with a PSA less than 4.0 ng/ml, 399/1205 (33.1%) underwent biopsy. Of these, 52 were found to have prostate cancer - 4.3% of the total group and 13% of those patients biopsied. *(24)* For the entire period of the trial, a prediction is much more difficult. For a trial design of 10 years in which accrual occurs during the first four years, an average follow-up of 8 years would be realized. From SEER data, this would be slightly in excess of 4%. However, SEER data may underestimate the actual diagnosis rate as patients would be followed much more closely than men in the general population. Indeed, prostate cancer incidence in Rochester, Minnesota increased dramatically after more general use of PSA in 1988. *(25)* The age-adjusted prostate cancer incidence rate for 1988-1989 was 2.5 times higher than for 1985-87. Thus, a more reasonable prevalence rate for the study duration may be as high as 10%.

The above process then could then entail the following:

1. Specify a PSA criterion applicable to the placebo group, (e.g. PSA > 4.0 ng/ml)

2. Estimate the % Yield for this criterion,

The next step in this process is to choose the corresponding criterion applicable to the finasteride group by using data from the North American Phase III clinical trials of finasteride to make the estimated percentage of % Yield (i.e., biopsy rate) in the finasteride group equal to the estimated % Yield in the placebo group. Thus, there would be two distinct PSA indexing procedures for the two arms of the study. These values of % Yield were computed limiting the population to the men with PSA less than 4.0 ng/ml at baseline and excluding men who were later found to have prostate cancer (about 1% of the total group).

The resulting criteria for the two groups meet the following requirements: (1) the estimated % Yield in the two study arms would be equal and (2) the positive predictive value in the placebo group would be at the desired level.

This system allows for an indexing of PSA for both placebo and finasteride arms of the trial such that at follow-up visits, assays for PSA would be sent to a Central Laboratory Facility and reported to the investigator as an 'indexed value'. In this study design, the baseline PSA value would be established at the six-month point after study entry. At this point, virtually all of the decrease in PSA due to the effect of finasteride would be realized. Thereafter, all values would be indexed to the six month value. If a change in PSA above that "allowed" by the above system were noted at any subsequent visit, further evaluation (with transrectal ultrasonography and prostate biopsy) would be required.

The above system is attractive as it attempts to counteract the change in PSA due to finasteride, continuing to 'allow' PSA to be a criterion for further evaluation. Unfortunately, despite the sophistication of the above analysis, too many major gaps in data exist. The most important of these is the suggestion that PSA may be more predictive of carcinoma of the prostate in patients treated with finasteride. The data which support this hypothesis are confidential and have been provided by Dr. Harry A. Guess, Senior Director of the Department of Epidemiology, Merck Sharp and Dohme Research Laboratories. *(26)* Using data from the North American Phase III trials, Figure 2 is a normalized rank plot. For each point on the graph, the horizontal axis shows the

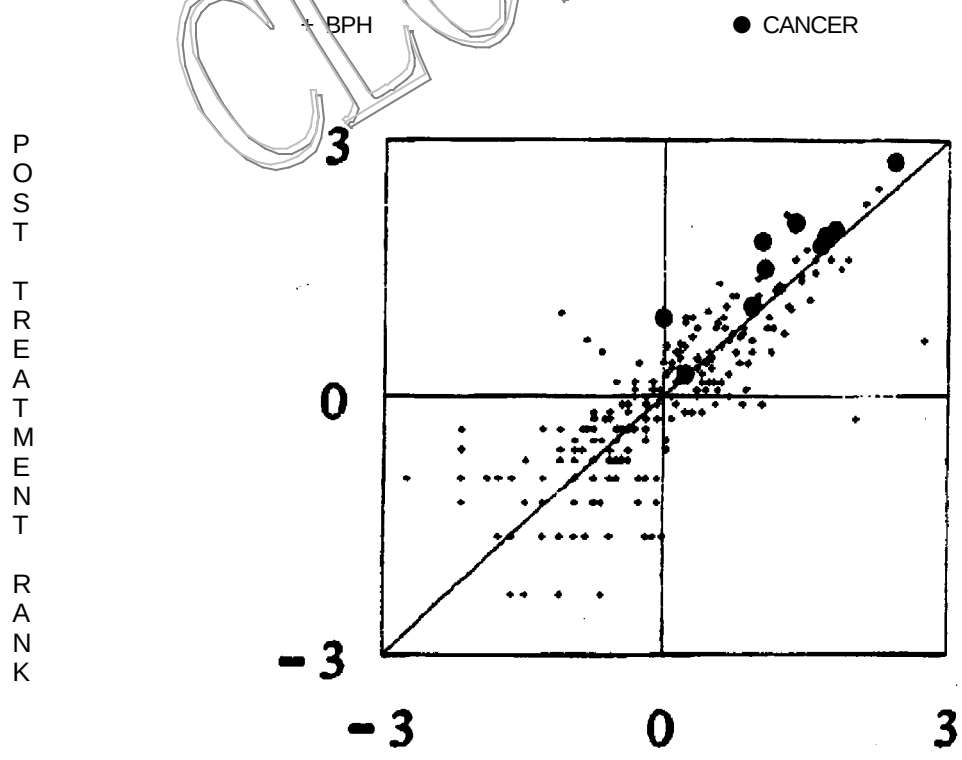
ranking of the patient's PSA at baseline, with the lowest ranking PSA's representing the lowest absolute values of PSA. The 0 point is the median of the pre-treatment PSA's (2.3 ng/ml). The vertical axis shows the ranking of PSA's after 12 months of treatment (1.2 ng/ml). Each patient's value is located on the graph by the horizontal and vertical coordinates representing, respectively, the pretreatment and the post-treatment rankings. Patients whose post-treatment rankings are greater than or equal to their pretreatment rankings fall on or above the 45° diagonal line. Patients whose post-treatment rankings are lower than their pretreatment rankings fall below the 45° diagonal line.

The large solid circles represent the ten men in whom prostate cancer was diagnosed while receiving 5 mg daily of finasteride in the North American clinical trials. All of these ten marks lie on or above the diagonal line. This means that the relative PSA ranking of these men after treatment with finasteride is greater than or equal to their relative ranking before treatment with finasteride.

Even though the numbers of prostate cancer patients on which these data are based are quite small, there seems to be a tendency for less of a percentage reduction in PSA among men with cancer relative to the percentage reduction in PSA among men with BPH and no prostate cancer. If this trend were borne out by larger numbers, it could be expected that biopsy of all men whose PSA's fell in the top "x" percent of the two groups would yield a greater number of cases of prostate cancer in the finasteride-treated arm, **irrespective of the actual rate of disease**. Thus, this factor could potentially bias this study design against finasteride and potentially lead to an erroneous acceptance of the null hypothesis. On the other hand, if PSA is less predictive of cancer in the finasteride group, there could be a bias in favor of finasteride.

Figure 2

PSA Normalized Ranks
Before and After Finasteride Treatment



STUDY DESIGN #3. Multiple Biopsies in Vanguard Group.

A recurrent theme in the design of a chemoprevention trial for carcinoma of the prostate is the lack of information on the operational characteristics of PSA over a prolonged period of time and the correlation of this assay with histologically-evident carcinoma. This study design has the advantage of correlating PSA with biopsy-proven disease and then applying these data to the detection efforts in the study population.

This trial design, again based upon the primary objective of determining whether finasteride reduces the incidence of carcinoma of the prostate, employs a Vanguard Group of 10% of the total study group. Participants entering the study would be men over age 55 who have a normal DRE and a PSA less than 4.0 ng/ml. Participants in the Vanguard Group would undergo annual evaluations with DRE and PSA which would be assayed in a Central Laboratory Facility. (CLF) Periodically, (e.g., years 1, 2, 4, 6, 8, and 10) all men in the Vanguard group would undergo prostate biopsy. As the men in the Vanguard group would always be one year ahead of the main body of the study population, PSA could be compared with the results of prostate biopsy at each of these points. As an example, at the one year mark, all men in the Vanguard Group would undergo PSA and prostate biopsy. From these data, the sensitivity of various levels of PSA for the detection of prostate cancer could be determined. For each level of sensitivity, a positive predictive value could also be determined. Using an "acceptable" PPV for prostate biopsy (e.g., in the 20 - 25% range), the corresponding sensitivity could be determined for the placebo group. This could then be translated into the finasteride group to calculate another PSA level (or "index") which would have the same sensitivity for the detection of prostate cancer. Thus, as the main body of participants were seen for the one year follow-up mark, PSA assays, sent to the CLF, would then be reported as "high" or "normal", based upon the Vanguard Group's experience. This system would then provide a mechanism by which the sensitivity of PSA would be identical in both groups.

This study design, again using as the primary objective the detection of a reduced incidence of carcinoma of the prostate in participants treated with finasteride, is perhaps the most scientifically-sound design, short of an annual biopsy in all men on the study. Unfortunately, there exist a number of significant variables and biases which cannot be addressed in this design with currently-available data.

The first problem with this study design is that during each year of the study, only a very small number of prostate tumors would be detected. Assuming a 2% detection rate at one year in the Vanguard Group and 1,000 men in each arm of this group, only 20 tumors in each arm would be detected. From these participants and a small group of participants with benign biopsies who have elevated PSA values, an indexing system for PSA would be designed. Unfortunately, such a system would have a large level of uncertainty which would then be magnified as it was extended into the ten-fold-larger main body of the study participants .
e biopsy is the gold standard for the detection of prostate cancer. It is well-established that there can be a significant sampling error and that some participants with a negative prostate biopsy who are rebiopsied would be found to harbor disease. Thus, due to chance, an increased variability of the biopsy-confirmation of the disease would be injected into the Vanguard Group.

An unusual problem with the design of a study using finasteride and combining it with serial prostate biopsies is that this agent leads to a significant reduction in prostate gland volume. This average 20% gland reduction, combined with a set method of prostate biopsy (e.g., sextant core biopsies under ultrasound guidance) would then lead to an increased percent of gland volume biopsied in participants treated with finasteride. Data are currently available to calculate volume of the peripheral zone of the prostate and to correct for changes in prostate volume. However, such a correction system would suffer from the poor reliability of volumetric imaging and would be exceedingly complex in a large cooperative trial. These problems would inject further uncertainty of unknown magnitude into the result.

The final problem with this chemoprevential trial design is that it is again unable to address the issue of a differing rate of detection of prostate cancer in finasteride participants due to a change in DRE. As elaborated above, this change in the gland texture could conceivably lead to a small increase or decrease in the detection rate in finasteride participants. At this time, it appears from the data in patients with BPH treated with finasteride or placebo, that such an effect is small in this class of patients. However, the change which could be expected in healthy men with a normal DRE is unknown.

STUDY DESIGN #4: Mortality or Metastatic Disease Design - Simplified Follow-up.

The designs listed above are similar in that they are all based upon the primary study objective of a reduction in incidence of the disease. This objective would be appropriate for several reasons: (1) it would lead to the greatest hazard rate (greater than mortality or metastatic disease as endpoints) and would therefore require the fewest number of participants, and (2) would not be affected by early study closure due to earlier endpoints. However, this endpoint has serious flaws, one of which is that clinically-evident carcinoma of the prostate does not always lead to metastatic disease nor death due to the disease. Several recent series of patients with prostate cancer in whom no treatment was provided, demonstrated that a large number of patients did not die of prostate cancer but of other causes. *(27)* The most recent of these series also demonstrated that the morbidity due to prostate cancer in those patients who did not develop metastatic disease was quite low. *(28)* Thus, the choice of incidence as the primary endpoint of this study of chemoprevention could be faulted as the difference detected may not be clinically-important to the patient.

An alternative endpoint for a chemoprevention trial would be mortality from the disease. This endpoint is attractive as cause-specific mortality is the most clinically-relevant of all potential endpoints. Such an endpoint would not be affected by the detection of unimportant (e.g., "latent", "occult", Stage A1) tumors or those tumors which were detected but which would have caused no ill effects during the participant's lifetime. A reduction in cause-specific mortality would then be of important consequence to the participant at risk.

There is a serious problem with the use of disease-specific (or overall) mortality in carcinoma of the prostate - early detection of differences in incidence which might prompt trial closure before the mortality endpoint could be reached. As an example - in a trial using finasteride for chemoprevention of prostate cancer and in which PSA is uncontrolled, it could be predicted that biopsies would be more common in participants who do not receive finasteride and, as the detection rate virtually parallels the numbers of biopsies, the incidence would be higher in the control arm of the study. This difference may be recognized very early in the trial. Once this point is reached, unless some control is placed over this event, serious consideration must be given for study closure. Such a closure might then mandate crossover of all participants on placebo to finasteride and the conclusion would be reached that finasteride significantly reduces the incidence of prostate cancer.

One mechanism to overcome this problem is to recognize at the study's inception that there would be a differential detection rate. This rate can be approximated by current PSA data and a highest-acceptable difference be established at the outset. During the trial, a Data and Safety Monitoring Committee could be charged with the follow-up of this difference and if it is exceeded, consideration be given for study closure. On the other hand, if this difference is not exceeded, participants would be continued on the two arms of the study with data collected for the primary endpoint: overall and disease-specific mortality.

A simplified mortality or metastatic disease trial would include a similar group of participants - normal digital rectal exam and normal PSA. At study entry, a demographic instrument would be administered. Participants would then be randomized to finasteride or placebo. Follow-up examinations for prostate cancer would be left to the standards of care within the participant's community and would not be dictated by the study design. At six month intervals, at the time of study drug refill, a questionnaire would be administered. An acceptable increased rate of prostate

cancer detection in the placebo group would be allowed and the Data and Safety Monitoring Committee would be charged with the responsibility of determining if early study closure was necessary. As the early detection of prostate cancer has not been established to decrease metastatic disease or mortality from the disease, such different rates of disease were felt to be acceptable in the two arms.

Although this study design is appealing, it suffers from several serious flaws. One is that, in the absence of a mandatory method of follow-up for cancer detection, a major detection bias could occur due to the significant difference in PSA in the two groups. This different detection rate could negate an otherwise significant decrease in prostate cancer mortality due to finasteride or could increase treatment-specific morbidity and mortality in the placebo group. A second major problem would be an almost certain drop-in rate among men on placebo. Men who were aware of their PSA value prior to study entry could easily determine their randomization drug by an off-study PSA. The lack of PSA monitoring and a mortality/metastatic disease endpoint could cause a significant number of men on the placebo arm to begin finasteride. A major drawback to this study design is its size. Using a 50% relative risk reduction, a 5% two-sided alpha, and an 80% power, a sample size of 24,000 would be required. Even a 40% relative risk reduction, 5% two-sided alpha with a 90% power requires a sample of 51,000. With more realistic relative risk reductions in the 25% range and with 90% power, sample sizes approaching or exceeding 100,000 may be required. Finally, as prostate cancer mortality accounts for only 3% of all deaths in men over the age of 55, in practical terms, a mortality study of 20,000 men would be an exercise in detecting a 22 death difference between treatment groups. The size of study required using this design would clearly be unmanageable and, with the multiple drawbacks discussed above, would suffer from serious scientific design flaws.

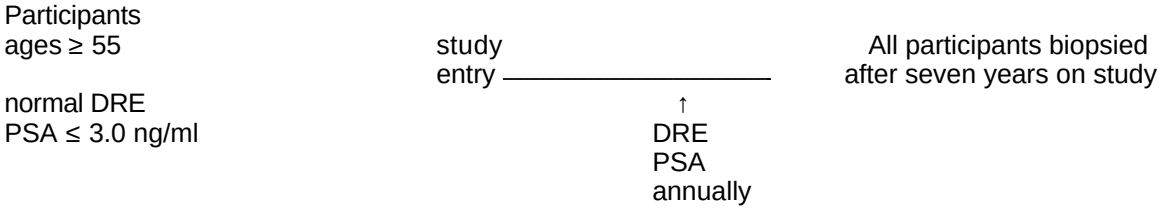
Summary of Study Designs - Final Design Selection

Each of the aforementioned four trial designs suffers from multiple flaws. Although a "perfect" trial design for this enigmatic disease is probably not possible, the inherent difficulties with the above four are sufficiently significant as to make any conclusions impeachable.

One major concern with all studies is the seriously-small hazard rate. This is most evident in the mortality rate design where as few as 210 cancer deaths might occur in 19,250 men receiving placebo who are followed for 10 years. This problem may be less serious but would remain operational in incidence trials. As it is known that over 30% of men over age 50 harbor prostate cancer but that fewer than 3% per year are detected with carcinoma of the prostate with intensive DRE/PSA screening programs, a large fraction of these men remain undiagnosed. *(22)* The proportion of these occult tumors which subsequently become biologically active is unknown. Thus, even with aggressive screening tests, the majority of prostate tumors remain undiagnosed. Additionally, in any study employing any form of screening test (e.g., PSA, DRE), several potential confounds are at work to potentially bias detection either **for** or **against** finasteride.

Due to these design concerns, a prototype trial design was envisioned. (Figure 3)

Figure 3



The design in Figure 3 has one primary advantage: all participants undergo biopsy after seven years on study. Potential detection biases between the study arms are minimized if all participants are biopsied. The most scientifically-sound variation of this study would be a prolonged interval (e.g., seven years) between entry and subsequent biopsy and during this time, no additional

screening tests would be performed. Although scientifically sound, in the opinion of a panel of active clinical urologists, participants or their physicians would be unwilling to enter such a randomized trial without interval cancer detection studies. Similarly, in accordance with the current clinical climate, few urologists would support such a trial.

A second variation of this design would be to elect the shorter duration between entry and biopsy without PSA or DRE in the intervening period. Although this design would alleviate participant concerns about interval screening, any biologic effect of finasteride, administered over two or three years (at most), might go undetected.

The final study design selected for this trial is a combination of a scientifically-sound protocol and one acceptable to a large participant population. In overview, it will consist of seven years of follow-up during which participants randomized to receive either placebo or finasteride are followed with annual DRE and PSA. Prostate biopsy would be prompted during follow-up of participants who are receiving placebo for an abnormal DRE or a PSA greater than 4.0 ng/ml. Biopsy of finasteride participants would be required for an abnormal DRE or an elevated PSA. (The PSA would be blinded such that the same percentage of participants in the finasteride group would undergo PSA-driven biopsy as the percentage in the placebo arm of the study.)

A number of biases could potentially be operational including "biopsy bias" (a smaller finasteride-treated gland with a larger percentage of the gland volume undergoing biopsy) and "DRE bias", but these would be minimized by the required final biopsy of **all** participants - an estimated 10-fold or larger number than those undergoing biopsy during the study.

The primary objective of this trial will be to determine if finasteride can reduce the development of carcinoma of the prostate in men aged 55 and older. Although this is a "chemoprevention" trial, it must be recognized that if such an effect is detected with the study drug, it may be due to a decrease in (1) tumor initiation, (2) promotion, or (3) merely due to decreased progression rate in a population of men with a relatively high risk of occult disease. Recognizing that any of these effects would be beneficial to the population at risk, this study is undertaken.

The upper limit of age for study eligibility will be based upon the physician's assessment of a participant's medical status. As all participants will undergo prostate biopsy seven years following study entry, only those participants in whom treatment for prostate cancer if biopsy proves positive at this time will be eligible for entry. As an example, although a 73 year old male may potentially be a candidate for therapy at that age, he may not be an appropriate candidate for enrollment, as the same positive prostate biopsy at age 80 may not prompt any form of therapy due to the participant's advanced age.

PSA Index

At years 1 - 6 following randomization, all participants will have a PSA screening for prostate cancer. Consider a placebo arm participant at the first screening, Year 1 from randomization. PSA for this participant will be reported as "elevated" if it is ≥ 4.0 ng/ml. Since finasteride lowers the PSA, a PSA index is required to impose a comparable cutoff for the finasteride arm to ensure that an equivalent number of finasteride arm participants are biopsied due to PSA. Without an index, the same cutoff of 4.0 ng/ml would reduce the sensitivity of the PSA screening on the finasteride arm.

A critical assumption that is needed to make the PSA Index valid is that finasteride reduces the PSA of each participant by the same percentage. This percentage can be estimated from Merck's data on BPH patients treatment with finasteride. Their data indicates that the finasteride arm PSA median will have been reduced by 48% of baseline at Year 1 (95% confidence interval 45 - 52%). *(51)* Using the Merck data, the PSA Index (factor) for the finasteride arm will be (1 - .48) (4.0) = 2.

Since the Merck data involved men with possibly different biological characteristics the factor of 2 will be used only for the initial estimate of the PSA Index in the PCPT. During the course of the PCPT, the PSA Index will be revised based on study estimates of the percent reduction in PSA

on the finasteride arm. The timing of the first estimate will be set such that a sufficient sample size is available to obtain an accurate estimate, say to within ± 5%. Subsequent estimates, given a greater sample size, will be more accurate.

Each participant has the potential of a PSA-induced prostate biopsy at each year of treatment. Once a participant has had a negative PSA-induced prostate biopsy, however, the criterion for a PSA-induced prostate biopsy changes. Consider a placebo arm participant at the second screening. Year 2 from randomization, who had a negative PSA-induced prostate biopsy at Year 1. PSA for this participant will be reported as "elevated" under the following conditions: 1) PSA ≥ 10 ng/ml, or 2) ≥ 50% increase over the previously reported "elevated" value. For the first condition, if we make the assumption again that PSA is reduced by 48% for each participant, the repeat biopsy PSA index for the finasteride arm will be (.48) (10) = 4.8 ng/ml. For the second condition, since a percent change in PSA has the same meaning on both arms, a ≥ 50% increase in PSA will also be an indication for a repeat biopsy on the finasteride arm.

The expected PSA-induced biopsy rate can be estimated from existing data. A total of 21,797 men were screened for prostate cancer as part of the Prostate Cancer Awareness Week. *(52)* The combined biopsy rate due to DRE and PSA was 5.2% (95% confidence interval 4.9 - 5.5%). Therefore the percent of men screened with a PSA ≥ 4.0 ng/ml was ≤ 5.2%. In a Minnesota screening study, 28/305 men of age 50 - 79 had a PSA ≥ 4.0 ng/ml for a rate of 9.2% (95% confidence interval 6.2 - 13%). *(53)* Another study from Abbott reported 5/394 (1.3%) of healthy men of age > 40, and 118/520 (23%) of men with BPH, prostatitis, or other genitourinary diseases had a PSA ≥ 4.0 ng/ml for a combined rate of 14% (95% confidence interval 11 - 16%). *(54)*

Study Features

A Touch-Tone telephone system at the Southwest Oncology Group Statistical Center will be used to randomize participants. The Southwest Oncology Group will create and supply each Study Center with a Study Manual. Training will be mandatory for designated personnel at all Study Centers. Training will take place prior to study activation. Additional training may be required as the study progresses.

The primary mechanism for submitting data forms to the Southwest Oncology Group Statistical Center will be via facsimile transmission. In some instances postal services may be utilized. The Southwest Oncology Group Statistical Center will communicate with participating Study Centers and/or Study Sites using facsimile transmission and postal service. Statistical Center communications will include information regarding follow-up schedules. Details regarding data submission, corrections and follow-up are found in the Study Manual.

Quality of Life

It is generally recognized (and it is Southwest Oncology Group policy) that assessment of quality of life (QOL) must involve measurement of multicomponents of a person's functioning. *(29 - 35)* There is consensus that QOL encompasses physical, role, emotional and social functioning, and symptom status and that it is important to assess these dimensions not only in cancer clinical trials but in any type of randomized clinical trial. Study participant report of QOL is required because it conveys additional information not present in the clinical report of how the individual is functioning. The reality of this additional perspective has been documented in research addressing the extent of agreement in physician and patient report of patient functioning. *(36 - 40)*

Multidimensional assessment of QOL is just as important and informative in chemoprevention trials. For example, QOL is assessed in the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) currently being conducted by the National Heart, Lung and Blood Institute (NHLBI). Goals of this research include assessing the protective effect of postmenopausal hormonal interventions for coronary heart disease; the role of such intervention in preventing osteoporosis

is a secondary research question. QOL is also being assessed in the Breast Cancer Prevention Trial (BCPT) of tamoxifen (National Surgical Adjuvant Breast and Bowel Project P-1 Protocol). In both instances, QOL is assessed with a battery of measures. The BCPT is using the Medical Outcomes Study Short Form-36 (MOS SF-36), the primary QOL measure proposed for this study.

The MOS SF-36 is based on health status scales developed by the Rand Corporation for the Health Insurance Experiment in the 1970's. These scales were designed to assess multiple dimensions of health status and functioning in a healthy population. *(41)* Subsequently, these health status scales were revised and shortened for use in clinical trials with both healthy and sick populations; the psychometric properties of these scales have been amply documented. *(35, 42 - 44)* The MOS SF-20 and SF-36 are currently in use in many trials involving medical interventions; MOS SF-20 and 36 scales are currently being used in several Southwest Oncology Group trials. The MOS SF-36 has separate scales and items (which are not summed for a total score) to measure overall perception of health, change in health status, pain, physical, role, social, and emotional functioning, and energy/fatigue. We believe that the MOS is ideally suited for assessing the effects of finasteride on the health status and QOL of healthy men participating in this chemoprevention study.

Protocol- or treatment-specific items will also be included in other QOL assessments to measure the effect of finasteride versus placebo on the sexual functioning of study participants since the most frequently reported side effect of this treatment has been some degree of sexual dysfunction. The American Urological Association (AUA) Symptom Index will be administered as well. *(45 - 47)* The sexual functioning questionnaire, the AUA Symptom Index, and the MOS - SF will be administered according to the Study Calendar (Section 9.0).

Brief baseline demographic and lifestyle questionnaires will be administered once to all participants (see Study Calendar, Section 9.0).

Recruitment of Participants

The planned recruitment support for the PCPT will involve activities at three levels: national (NCI), centralized (Southwest Oncology Group), and local (Study Centers). The NCI has pledged the support and involvement of the Office of Cancer Communications in the development and distribution of press releases. Their cancer information telephone line will direct interested callers to the nearest Study Center. The Southwest Oncology Group will be responsible for the following: training Study Center staff through mandatory specialized PCPT Training Workshops; developing publications, videotapes, newsletters, press releases, and other materials for distribution to Study Centers.

The Southwest Oncology Group will provide Study Centers with packets of materials to facilitate recruitment of study participants. These materials will address generic recruitment strategies, but will also target strategies appropriate for the African-American male audience. A videotape will also be included, as well as brochures which may be distributed in the community. More specifically, recruitment procedures will address the following approaches to identifying and involving potential participants: contacting male relatives of existing prostate cancer patients (including non-clinical trials cancer patients); obtaining referrals from prostate cancer screening clinics; developing referral patterns from physicians (family practitioners, urologists, etc.) likely to care for men meeting study eligibility criteria; making presentations and/or distributing materials to appropriate groups of men (e.g., through church and community groups); and, conducting local media campaigns. A study recently conducted by Eisner and Tobin of the NCI found that television was considered a preferred way for men to obtain information about prostate cancer and prostate cancer screening. *(48)* A focus group approach was used to discuss these issues with the male and female study participants. This study also concluded that "significant others" presented another appropriate mechanism for reaching male candidates at risk for prostate cancer.

Regarding the content of materials, both the Eisner and Tobin study and studies conducted by others working in this field (Personal Communications: Ronald Myers, Ph.D., D.S.W.; Jeanne

Parzuchowski, R.N., M.S., O.S.N.; Edward DeAntoni, Ph.D.; October 1992 through January 1993) indicate the need for materials to address the following types of issues, particularly for African-American males: trust, with respect to participation in an "experiment" (i.e., participants' perception of being used as "guinea pigs"); factual information regarding the drug and possible side effects on sexual functioning; pain and discomfort associated with examinations required for participation; embarrassment and privacy factors; and, information source credibility. Although most of this information is based on studies and focus groups regarding the issue of screening for prostate cancer, it provides a starting point for recruitment and educational efforts to be emphasized in this trial. Materials addressing these issues will be subjected to expert consultant review prior to production and distribution to the Study Centers.

In addition, the Southwest Oncology Group will distribute a supply of participant newsletters to all Study Centers for subsequent distribution to the participants by these Study Centers. These newsletters will be targeted towards the participants themselves, and may contain information regarding support group meetings/activities developed by Study Centers, as well as progress reports on accrual. The participant newsletter will also provide reminders to the participants to encourage adherence. Articles on prostate cancer and cancer prevention in general may also be included. Study Centers may also include local interest items as an attachment to this newsletter, prior to distribution to their local participants.

Cardiovascular Assessments

In men over the age of 55, cardiovascular diseases are anticipated to occur 3 to 5 times more frequently than prostate cancer. In addition, approximately 1 of every 2 deaths recorded in men of this age are expected to be associated with cardiovascular disease. To monitor and interpret cardiovascular adverse drug reactions and deaths adequately, cholesterol measurements are obtained at the First Visit to characterize each participant's risk status. Using guidelines from the National High Blood Pressure Education Program, men will be classified as high risk, borderline high risk, or normal risk. *(50)* In line with the National Cholesterol Screening Guidelines, men who are found to have abnormal screening cholesterols will be appropriately referred for further evaluation and/or treatment. As a benefit to their participation, this adherence to National Screening Guidelines will assist healthy recruits in reducing their risk of heart disease.

Dietary Assessment

Dietary assessment will be a one time data collection at the first Annual Visit using a self-administered Food Frequency and Nutritional Supplement Questionnaire. A validity study of the questionnaire will be completed using a small subset of participants during the period of time between their first Annual Visit and the second Annual Visit. In addition, adiposity and body fat distribution will be assessed by four anthropometric measures taken at the first Annual Visit. See Appendix I of the Study Manual and Appendix 19.7 of the protocol for details.

CAG Repeat Length

This study will assess the degree to w hich CAG trinucleotide repeat length is associated with an increased risk of prostate cancer. See Appendix 19.8 of the protocol for details.

3.0 DRUG INFORMATION

3.1 Finasteride (Proscar™) (IND-28422)

a. DESCRIPTION:

Chemistry: Finasteride, N-(1,1-dimethyl)-3-oxo-4-aza-5a--androst-1-ene-17β-carboxamide, is a neutral 4-azasteroid of empirical formula, C23H36N2O2.

Finasteride, also known as Proscar, MK-906, or L-652,931, is a 4-azasteroid competitive inhibitor of human 5-alpha reductase. Five-alpha reductase is a nuclear membrane bound NADPH dependent delta-3-ketosteroid 5-alpha-oxidoreductase. It is found in androgen sensitive tissues; e.g., skin, liver and prostate. The enzyme catalyzes the conversion of testosterone (T) to dihydrotestosterone (DHT). Finasteride inhibits the conversion of T to DHT. Finasteride does not inhibit the binding of DHT to the androgen receptor. There are two known isoenzymes of 5-alpha reductase: Type I predominates in peripheral tissues while Type II predominates in the prostate. Studies thus far have demonstrated that finasteride is more efficient at inhibiting the Type II than that Type I isoenzyme of 5-alpha reductase.

b. TOXICOLOGY:
In animals the LD50 is greater than 370 mg/kg. At toxic doses, reactions included ataxia, bradypnea, decreased activity, loss of righting, lacrimation and tremor. In vitro studies showed no evidence of mutagenicity or teratogenicity.

Human Toxicology: Safety data has been extracted from a study including 2,453 patients with at least one dose of finasteride and 962 patients on placebo. Median duration of this study was 322 days. 40/2,453 or 1.6% of patients discontinued finasteride due to adverse experience. Impotence was the most common complaint for drug discontinuation. Impotence (3.7%), libido (3.3%), and ejaculatory disturbances (2.9%) were the most common side effects. Other reactions included abdominal pain and upper respiratory infections. Laboratory changes included increase in BUN (without increase in creatinine), neutrophils, and serum glucose. Subsequent study showed that finasteride does not affect glucose tolerance. Since marketing, Merck has received a small number of reports consistent with hypersensitivity reactions. Twelve reports of facial edema or angioneurotic edema and 39 reports of rash have been received. Reports suggestive of hypersensitive reaction have generally been mild, but in a small number of reports rechallenge has been positive. Since marketing, Merck has also received reports of breast enlargement and/or tenderness.

c. PHARMACOLOGY:
Kinetics: When 5 mg of finasteride was given PO to healthy male volunteers, peak plasma level was 37 ng/ml with elimination half-life of 6 hours. Studies revealed that the oral bioavailability of the drug was 80% of an IV administration of finasteride. Plasma concentration of the drug was proportional to the dose up to 50 mg. In normal male volunteers, 30% of finasteride was excreted in the urine as metabolites, with no unchanged drug excreted. Fifty-seven percent was excreted in the feces. With renal impairment, although less of the metabolite was excreted in the urine, there was a proportionate increase in fecal excretion. Plasma clearance was 165 ml/min. Co-administration of food did not affect disposition of finasteride.

Since finasteride is metabolized by the liver, drug interaction studies were done. These studies revealed no changes in the metabolism and/or disposition of anti-pyrines, digoxin (single dose), propanol, glyburide or warfarin. Glucose and insulin responses to an oral glucose tolerance test were unchanged.

Although clearance after a single dose of aminophylline was 7% higher with administration of finasteride, this was felt to be insignificant.

Males with congenital deficiency of 5-alpha reductase exhibit ambiguous external genitalia at birth, scant facial hair as adults and underdeveloped prostate gland. Finasteride has no antiandrogenic, antiestrogenic or antiprogestational effects. Finasteride does not affect testosterone dependent functions such as maintenance of muscle bulk, sexual function and libido.

Early, short-term clinical pharmacology studies demonstrated that finasteride, at doses as small as 0.04 mg/day for 14 days, resulted in a decrease in serum DHT to levels 63% of baseline, with the effect noted at 24 hours following the first dose. DHT levels returned to baseline approximately two weeks after cessation of therapy. PSA levels are reduced in patients receiving finasteride. In a small study of asymptomatic men with metastatic prostate cancer, PSA levels were reduced by 22.9% and 15.1% at 3 and 6 weeks of therapy, respectively. At 24 weeks of therapy, PSA had attained a 31% reduction in value.

In studies of men with benign prostatic hyperplasia, the toxicity of finasteride was minimal. At a dose of 5 mg/day, DHT was suppressed to 80% of baseline as was intraprostatic DHT. Prostatic volume was reduced by 20% in 50% or more of the patients by one year of therapy with a continued reduction in gland size over the

second year of therapy. Urinary flow rate in these patients increased significantly, thus improving symptoms of bladder outlet obstruction.

Formulation: 5 mg tablets

Storage and Stability: **Store at room temperatures between 59° and 89° F. If the film coating of the tablets has been broken (e.g., crushed), the tablets should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of the drug and the subsequent potential risk to a male fetus.**

Administration: PO, administered as a single daily dose

Supplier: Finasteride will be packaged, labelled and supplied by Merck-Sharpe and Dohme. Finasteride, 5 mg or matching placebo will be packaged for participants in bottles each containing either 130 tablets (3 month supply) or 200 tablets (6 month supply). Bottles of finasteride or placebo will be labelled with the participant's drug identification number and the packaging code number. Instructions will be: "Take one tablet daily."

A supply of medications (enrollment drug and study drug) will be sent to each Study Center upon study activation. Subsequent study drug for each patient and additional supplies of medications will be sent automatically based on individual Study Center accrual projections submitted to the Drug Distribution Center. For problems, questions, or to request emergency drug shipments call (800) 370-2508, Monday through Friday 6:00 a.m. - 5:00 p.m., Pacific Standard Time. Voice mail is available at all other times. All unused medication will be returned, accompanied by a Form 409-Returned Medication Packing Slip to Axion Pharmaceuticals, Inc., the Drug Distribution Center for the study. See the Study Manual for more information.

4.0 STAGING CRITERIA

Staging Criteria are included in Appendix 19.2 as a reference for staging participants who develop prostate cancer while receiving protocol treatment.

5.0 ELIGIBILITY CRITERIA

Enrollment Criteria

5.1 Participants must be male, ages 55 or older. Participants must be of such an age and medical condition that the physician would anticipate treatment of a prostate tumor detected within seven years following study entry. If a participant would be of an advanced age or of an anticipated medical status such that diagnosed prostate cancer within seven years following study entry would not require treatment, the patient is ineligible.

5.2 The participant must have a performance status of 0 by Southwest Oncology Group criteria (see Section 10.3).

5.3 The participant must be able and willing to participate in the full seven years of study treatment.

5.4 Participants must have a Digital Rectal Examination (DRE) **WITHIN NORMAL LIMITS** (without induration, asymmetry, prostate nodularity). DRE must be performed within 28 days prior to enrollment.

5.5 The specimen for PSA must be drawn within 28 days prior to enrollment and sent to the Central Laboratory Facility (CLF). For participants with prostatitis and/or other clinical situations expected to raise the PSA value, it is recommended that enrollment be postponed for two months following resolution of the clinical condition.

5.6 Individuals previously diagnosed with prostate cancer or Prostatic Intraepithelial Neoplasia (PIN) are ineligible.

5.7 Individuals are ineligible if they have a prior history of malignancies other than basal or squamous cell carcinoma of the skin within the past five years. Individuals are eligible if they have had a prior malignancy but have had no evidence of disease for at least five years prior to registration.

5.8 Individuals must not have received prior finasteride or anabolic steroids for any reason. Individuals must not have received prior hormonal therapy, chemotherapy, biologics or radiotherapy as treatment for cancer.

5.9 Individuals must not be in urinary retention.

5.10 Individuals desiring immediate medical or surgical treatment of urinary obstructive symptoms are ineligible. Individuals must not have had a transurethral resection of the prostate (TURP) less than six months prior to enrollment.

5.11 Individuals with severe prostatism as manifested by an AUA symptom score of 20 or greater are ineligible.

5.12 Individuals currently receiving anticoagulation therapy (e.g., coumadin) are ineligible. Individuals currently taking aspirin as anticoagulation therapy are eligible.

5.13 Individuals with other medical illnesses which, in the investigator's opinion, cannot be adequately controlled with appropriate therapy, including, but not limited to myocardial infarction within the previous three months, active angina, unstable heart rhythms, clinically evident congestive heart failure, uncontrolled diabetes, and peptic ulcer disease which is uncontrolled by medical management are ineligible.

5.14 Individuals who are known to be HIV positive are ineligible.

5.15 Individuals who are participating in any other clinical trial are ineligible.

5.16 Men may not participate unless they have agreed to use an effective contraceptive method. If the sexual partner is pregnant or becomes pregnant during the course of the man's participation in this study, the participant must agree to use a contraceptive method which would prevent the exposure of his sexual partner to semen. This precaution is taken because of potential risk to a male fetus.

5.17 All participants must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.18 At the time of participant enrollment, the date of institutional review board approval for this study must be provided to the Statistical Center.

5.19 Participants must have completed the baseline Form 201-Health Status Questionnaire (Health Survey SF-36).

NOTE: If the participant does not read and understand English or Spanish, this criterion and Section 5.20 do not apply.

5.20 Participants must agree to complete Quality of Life assessments as required.

5.21 The physical examination required for eligibility must be performed within 42 days prior to enrollment. All other pre-enrollment examinations, testing and evaluations required for eligibility must be completed within 28 days prior to enrollment.

Final Enrollment Criteria

5.22 Participants must have a PSA (prostate specific antigen) performed with monoclonal assay (as determined by the CLF from the specimen drawn at the time of enrollment) ≤ 3.0 ng/ml.

5.23 Participants with an increase of more than two toxicity grades over the baseline grade for symptoms of impotence, loss of libido, and ejaculate volume at the end of the three month enrollment period are not eligible for final enrollment (randomization). These toxicities must be assessed using the Supplemental Toxicity Criteria in Section 8.2 of this protocol. Participants with other Grade 2 or greater toxicities (as defined by the Southwest Oncology Group Toxicity Criteria) at the end of the three month enrollment period are ineligible for final enrollment (randomization). Dermatologic toxicities must be < Grade 3 for final enrollment.

5.24 Participants who fail to meet the enrollment medication adherence criteria are ineligible for final enrollment (randomization).

6.0 STRATIFICATION/RANDOMIZATION SCHEME

6.1 Participants will be described by: age (55 - 59 vs 60 - 64 vs ≥ 65) at enrollment, race (African-American vs other), and positive family history of prostate cancer in a first-degree relative (yes vs no).

6.2 Participants will be randomized to receive finasteride or a matched placebo. (See Study Manual for detailed enrollment and randomization procedures.)

7.0 TREATMENT PLAN

7.1 At the First Visit, potential participants who sign the consent form and meet the eligibility requirements for enrollment will complete appropriate study forms. Participants will be enrolled and given a three month supply of the enrollment drug. Initiation of treatment must begin within seven days. All participants will then begin the three-month enrollment period.

Risk factors for coronary heart disease (see Section 19.3) will be determined at the First Visit. Nonfasting total and HDL cholesterol will be measured on serum drawn at the First Visit by the Central Laboratory Facility (CLF) and reported back to the Study Centers. This test will be performed only on serum from participants who are actually randomized. If one of the following criteria are met, participants will be referred for additional evaluation:

Total Cholesterol > 240, or
Total Cholesterol 200 - 240 and participant has had a definite prior myocardial infarction or myocardial ischemia such as angina pectoris, or
Total Cholesterol 200 - 240 and participant has ≥ 2 other risk factors (see Section 19.3).

7.2 Three months later, participants will return to the Study Center for the scheduled Second Visit, and will be assessed for medication adherence, PSA value and side effects. Non-adherent participants (based on pill-counts), those desiring to terminate study participation, those with a PSA > 3 ng/ml, or those with side-effects (as defined in Section 5.23), or symptoms deemed unacceptable to the participant will not be randomized and will be considered incomplete enrollments. (Dermatologic toxicities must be < Grade 3 for final enrollment.) Participants who meet final enrollment eligibility criteria as defined in Sections 5.22-5.24 and who desire to continue on-study will be randomized to receive either finasteride 5 mg/day or a matched placebo, one tablet per day. An initial six-month supply of the study drug will be dispensed.

Pre-assigned numbered blocks of Enrollment Drug and Study Drug, treatment-placebo and treatment-finasteride bottles will be provided at study inception to participating Study Centers. At enrollment, the Study Center will assign the identification number of the Enrollment Drug from the set of pre-assigned numbers. During the randomization telephone call, the Study Center will be given the identification number of the Study Drug to be dispensed to the participant also from a set of pre-assigned numbers. (See also Section 7.13.)

7.3 Treatment must begin within seven days following enrollment and randomization.

7.4 Treatment Schedule Following Final Enrollment.

AGENT	DOSE	ROUTE	DAYS	DURATION
Finasteride or Matched Placebo	5 mg tablet	po	qd	7 years

7.5 Participants will be contacted for follow-up by telephone at three months after the Second Visit and at three months after each Study Center visit. Participants will return six months after the Second Visit and every six months thereafter. At each six month contact, study forms will be completed, participants will be assessed for adherence and symptoms/side-effects, and the next six month supply of the Study Drug will be dispensed. (see Study Calendar, Section 9.0)

7.6 On an annual basis following Final Enrollment, participants will undergo DRE and PSA determinations.

a. DRE: Digital rectal examination will be conducted by a medical professional skilled in identifying subtle abnormalities of the prostate. At the time of each DRE, the findings of the DRE will be recorded for reference at subsequent visits. If DRE is suspicious for prostate cancer because of nodularity, asymmetry, or induration, transrectal ultrasonography (TRUS) and prostate biopsy is recommended. Any biopsies performed are to be done in accordance with Section 7.7 and Appendix 19.5. The appropriate pathologic specimens must be submitted to the Pathology Core Laboratory as described in Appendix 19.4. If the biopsy is negative for prostate cancer, and there is an abnormal DRE at any subsequent visit a TRUS and prostate biopsy is recommended.

b. PSA: Randomized participants who are determined to have clinical evidence of prostatitis or other clinical conditions or situations expected to affect the participant's PSA level (i.e. prostatic abscess, TURP or laser ablation of the prostate) at the time of PSA serum drawing should have the PSA postponed. The PSA should be postponed for two months following the initiation of therapy for prostatitis, two months following resolution of any clinical condition, or two months following any procedure performed on the prostate.

Prior to obtaining PSA specimens, the degree of study drug adherence must be ascertained by PCPT staff. **This is *extremely* important because non-adherence immediately prior to specimen collection will affect the accuracy of the PSA Index. Non-adherence to the study drug that is not reported to PCPT staff may result in an unnecessary recommendation for prostate biopsy. This information is to be communicated to the participant**. If it is determined that in the two weeks prior to the visit that the participant has not taken any study drug, delay collecting the PSA specimen for two months.

Monoclonal PSA determinations will be performed in the Central Laboratory Facility (CLF) and will be blinded to participants and investigators. For both participants receiving finasteride or placebo, PSA determinations will be reported as either "NOT ELEVATED" or "ELEVATED". A numerical PSA value will be reported on all participants with an "ELEVATED" PSA at annual examination. The reported PSA values for participants receiving placebo will be the measured value. The reported PSA values for participants receiving finasteride will be adjusted by a factor calculated by the Statistical Center (with monitoring by the Data and Safety Monitoring Committee).

The adjustment factor will be calculated by first determining the percentage of placebo-treated participants with elevated PSA. Then, for the finasteride-treated participants, the value of PSA for which the same percentage of participants will be elevated will be identified. This value will be used to calculate the factor for adjusting the PSA for participants treated with finasteride. This method will prevent PSA bias between placebo- and finasteride-treated participants for whom a biopsy is recommended. Details of this procedure and justification can be found in the Background Section of this protocol under "PSA Index".

If the participant has an "ELEVATED" PSA a prostate biopsy (see Section 7.7) is recommended. Decisions regarding appropriate follow-up care for the participant should be based on this PSA value and the clinical judgment of the investigator. If a repeat PSA value is deemed necessary, the test *must* be performed by the Central Laboratory Facility. This is essential as, without knowledge of the participant's actual treatment, a value from an outside laboratory is meaningless.

Participants with an elevated PSA who have benign tissue upon pathologic examination by the Pathology Core Laboratory are recommended to have a TRUS and biopsy at subsequent years if one or both of two conditions are met: (1) PSA increase of 50% or more above the PSA value that prompted the recommendation of the original biopsy or (2) adjusted PSA greater than 10 ng/ml.

PSA values will be provided for participants who are off treatment. These values will not be indexed (adjusted).

c. All participants will be evaluated according to the AUA Symptom Scale annually.

d. All participants will complete a diet questionnaire and have physical measurements performed at the First Annual Visit only.

e. Participants who are removed from treatment for any reason other than development of prostate cancer will be followed twice annually for the remainder of the seven years. One contact will be by phone for a general health status update, and the other contact will be a Study Site visit for annual DRE and PSA. The requirements for endpoint reporting, management of abnormal DRE and/or "ELEVATED" PSA as well as pathology submission will be the same as for participants who remain on treatment.

7.7 Management of participants with abnormal DRE and/or "ELEVATED" PSA.

a. If at any time during follow-up, the participant is found to have a digital rectal examination suspicious for prostate cancer or an "ELEVATED" PSA, it is recommended that the participant undergo transrectal ultrasonography (TRUS) and prostate biopsy. **It is to be emphasized that the PCPT <u>recommends</u> that the participant and physician consider the TRUS and biopsy. The participant should be told of this recommendation and advised to discuss it with his physician when considering options for follow-up**. TRUS and biopsy must be performed within 28 days of the abnormal DRE or notification of an "ELEVATED" PSA. If , for any reason, a TRUS and biopsy is not performed, the Statistical Center should be notified per Section 7 of the Study Manual.

b. Any hypoechoic lesions noted on ultrasonography should be biopsied as well as any digitally notable lesions in addition to sextant biopsy. If no abnormalities are detected on ultrasound or digitally, sextant biopsy should be performed in accordance with Section 7.7c below. It should be emphasized that each participant undergoing biopsy will have at least six biopsies performed.

c. Technique of sextant biopsy: Transrectal ultrasound (TRUS) will be performed by a clinician experienced in this procedure. Using sagittal imaging, three core biopsies are obtained from the right and left sides at the level of the base, mid-gland, and apical aspects of the prostate. The needle path should be directed so as to maximize the sampling of the peripheral zone of the prostate as described by Hodge, et al. *(49)* Good Medical Practice guidelines should be observed at the time of the end-of-study prostate biopsy. Medications that interfere with normal coagulation should be discontinued for an appropriate period of time prior to prostate biopsy.

d. At the time of TRUS/biopsy, three measurements of prostate size will be recorded: maximum AP height, maximum width and prostate length.

e. Participants found to have high grade (Grade 2 - 3) Prostatic Intraepithelial Neoplasia (PIN) at the time of biopsy should undergo an immediate rebiopsy. The rebiopsy (using the sextant biopsy technique described in Section 7.7c) must be performed within two months of the prior biopsy. If the repeat biopsy is benign or reveals PIN, the patient will continue on protocol. If this biopsy reveals prostate cancer, however, the patient is removed from protocol treatment per Section 7.14.

7.8 After seven years on study, all participants still receiving protocol treatment will undergo transrectal ultrasound and prostate biopsy in accordance with Sections 7.7b, 7.7c and 7.7d.

7.9 Development of symptoms of benign prostatic hyperplasia.

During participant on study follow-up, should obstructive symptoms develop to such an extent that the participant requests therapy, the participant should be offered therapy in accordance with standard medical or surgical practice. At the time of such therapy (including medical or surgical therapy), the manner of treatment will be recorded on study forms. One of the options for medical therapy may be finasteride. If finasteride is chosen for therapy, the participant must be evaluated and removed from protocol treatment. For this reason, other forms of medical therapy such as alpha blockade should be encouraged.

7.10 Upon the diagnosis of prostate cancer, staging will be accomplished in accordance with standard clinical practice (see Section 19.2). PSA values for these participants who were biopsied because of an abnormal DRE and whose biopsy is positive for prostate cancer will be provided by the Statistical Center when requested by PCPT staff. The reported PSA value for participants receiving placebo will be the measured value. The reported PSA value for participants receiving finasteride will be adjusted by a factor calculated by the Statistical Center (with monitoring by the Data and Safety Monitoring Committee).

7.11 In all participants who undergo a surgical procedure in which prostate tissue is removed (e.g., prostate biopsy, TURP, radical prostatectomy), specimens will be submitted to the Pathology Core Laboratory for centralized pathology review in accordance with Section 12.0 and Appendix 19.4. The Pathology Core Laboratory will also serve as the Prostate Tissue Repository for these specimens. Sera for annual PSA determinations will be submitted to the Central Laboratory Facility; residual sera will be banked for future study in a serum bank to be maintained by the Central Laboratory Facility.

7.12 The Data and Safety Monitoring Committee will be charged with monitoring and evaluating potential detection bias during the study's progress. This committee may require interim DHT determinations and/or prostate biopsy (in accordance with Section 7.7) in a sample of participants to determine if such bias is operational.

7.13 Adherence.

Participant adherence with the medication regimen as well as the follow-up schedule is critical for proper study completion. Data Managers will contact participants every three months for the study's duration to assure medication adherence as well as to reinforce follow-up visit schedules.

Following randomization, tablet counts will occur every six months, i.e., each time the participant requires a new supply of Study Drug. All adherence information will be recorded on study forms. Details of, and procedures for, the assessments are found in the Study Manual.

7.14 Study Blinding Information and Criteria for Removal from Protocol Treatment:

a. All participants, Study Centers, pathology and laboratory personnel will be blinded to study treatment.

b. Laboratory and pathology specimens will be labeled by participant identification number and initials only.

c. Participants treatment will be unblinded only if the treating physician demonstrates a compelling medical need for this information. The study drug may be discontinued without unblinding the participant.

d. As study arms will be analyzed using an intent to treat method, participants are never "dropped" from the study.

e. Participants will be removed from protocol treatment under the following circumstances:

1. diagnosis of prostate cancer.

2. initiation of treatment for benign prostatic hyperplasia (BPH) with finasteride or other 5-alpha reductase inhibitor.

3. seven years following randomization (termination of the study).

4. intercurrent illness which would, in the judgement of the treating physician, affect assessments of clinical status to a significant degree and/or require discontinuation of drug. **Participants will not discontinue the study drug for other medical events which are not considered to be drug-related (e.g., cardiovascular event, diabetes). This determination will be made by the treating physician. The Data and Safety Monitoring**

Committee will monitor relative rate of these events for trends.

5. unacceptable side effects. The reason(s) must be documented on the study forms.

6. missed contacts. The participant missed receiving more than two consecutive bottles of study drug or missed more than four consecutive Study Site Visits.

f. Participants may be returned to protocol treatment (i.e., reactivated) if they meet the criteria for reactivation defined in Section 4.0 of the Study Manual.

7.15 The participant may withdraw from the study at any time for any reason. The reason must be documented in the study forms.

7.16 All participants will be followed off-treatment as required per Appendix Section 19.10.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 There will be no modifications to the study drug dose.

8.2 For decreased libido, impotence and decreased volume of ejaculate or any clinically acceptable symptoms potentially due to the study drug, participants should be requested to remain on study drug. If they refuse, they may be allowed to discontinue the drug. They should then be reassessed in three months. If the side effect has not resolved, the participants can restart the drug. If the side-effects improve, the participants should be re-challenged with the drug and if the side effect recurs, the drug should be discontinued permanently.

The PCPT will not use the new NCI Common Toxicity Criteria for the reporting of Adverse Drug Reactions/Adverse Events and routine follow-up. Please use the Southwest Oncology Group Toxicity Criteria in Appendix 19.1 for: 1) assessment of all symptoms (including those related to sexual function) for the purpose of reporting Adverse Drug Reactions/Adverse Event and for 2) assessment of symptoms not related to sexual function for routine toxicity reporting. For assessment of symptoms of sexual function for eligibility purposes and routine toxicity reporting, use the following criteria in lieu of those in Appendix 19.1.

Impotence:

Grade 1 decrease in normal function, able with difficulty to achieve vaginal penetration.
Grade 3 absence of function, no erections

Loss of Libido:

Grade 1 minimal decrease in desire for sexual activity, no impact on frequency of intercourse
Grade 2 moderate decrease in desire for sexual activity, minimal impact on frequency of intercourse
Grade 3 moderate to severe decrease in desire for sexual activity, moderate impact on frequency of intercourse
Grade 4 no desire for sexual activity, no intercourse

Ejaculate Volume:

Grade 1 less than 1/3 reduction in ejaculate volume (as perceived by the participant)
Grade 2 1/3 to 2/3 reduction in ejaculate volume
Grade 3 greater than 2/3 reduction in ejaculate volume
Grade 4 no ejaculate

8.3 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Southwest Oncology Group Operations Office, and to the IRB. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR

	Enrollment	Randomization	Post-Randomization Follow-Up				
REQUIRED STUDIES	**1st visit**	**2nd visit**	**3 and 9 month phone calls**	**6 month visits**	**Annual visits**	**Seven yr visit**	**Extended Follow-Up†**
Participant Demographics	X						
Contact Information	X	X	X	X	X	X	X
MEDICAL HISTORY							
Cancer	X						
Prior therapy	X						
Family history prostate cancer	X						
CHD risk factors *ƒ*	X						
Participant Lifestyles							
Smoking	X						
Alcohol Use	X						
Eating	X						
Exercise	X						
QOL - Health Survey SF-36	X			X*	X	X	
Food Frequency Questionnaire					XΩ		
Participant Report							
Urinary symptoms	X	X		X*	X	X	X
Sexual functioning	X	X		X*	X	X	X
Staff Report							
Adherence assessment		X		X	X	X	
Symptom/side effects assess.		X		X	X	X	
CLINICAL							
Performance Status	X						
Current medications	X	X	X	X	X	X	
DRE	X				X	X	X†
Physical Examination	X				X	X	X†
Anthropometric measurements					XΩ		
Prostate biopsy/TRUS √					X#	X	
LABORATORY							
Serum for PSA/cholesterol/	X£Δ				X£	X£	X†
and serum bank storage							
WBC Blood draw ∞							
Outcome Assessment							
Prostate Cancer		X		X	X	X	X
BPH		X		X	X	X	X
Other Cancer		X		X	X	X	X
Cardiovascular event		X		X	X	X	X
Death		X		X	X	X	X
TREATMENT							
Finasteride or matched Placebo		X	X	X	X		
Enrollment drug	X						

NOTE: All forms to be utilized for this study and forms submission guidelines are found in the Study Manual.

ƒ See Section 19.3 for CHD risk factors.

* Collected at first six month visit and then annually.

Ω Collected only at first Annual Visit.

√ With measurement of prostate size.

\# Performed only on participants whose PSA or DRE indicate; pathology submission is required.

£ Specimen mailed to and tests performed in Central Laboratory Facility (CLF).

Δ Non-fasting total cholesterol performed on serum drawn at the first visit only. If total cholesterol exceeds 200 mg/dl, patient referral for evaluation is required (see Study Manual).

∞ As outlined in Section 19.9.

† See Section 19.10 for the procedures related to Extended Follow-Up.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The primary endpoint of this study is histologically proven presence/absence of carcinoma of the prostate after seven years.

10.1 Survival is defined as the period of time between Final Enrollment and death of any cause.

10.2 Prostate cancer-specific survival is defined as the period of time between Final Enrollment and death due to prostate cancer. For staging criteria, see Section 19.2.

10.3 Criteria for Estimation of Performance Status: At the First Visit participants will be graded according to the current Southwest Oncology Group grading scale:

GRADESCALE

0	Fully active; able to carry on all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

NOTE: If the participant has a permanent disability that does not impair his ability to carry on all normal activities of daily living, he may be graded with a Performance Status of 0.

11.0 STATISTICAL CONSIDERATIONS

11.1 OVERVIEW: The primary objective of this prevention trial is to assess whether participants randomized to receive finasteride for seven years will have a different proportion of prostate cancer than participants randomized to receive a placebo for seven years. Other objectives of this study are listed in the Objectives section of this protocol (Section 1.0) and include estimation of the side-effect rates associated with finasteride, assessment of the acceptability of long-term finasteride use by healthy participants, and assessment of the effect of finasteride on the sensitivity and specificity of DRE and PSA.

A study of 18,000 randomized subjects (9,000 placebo, 9,000 finasteride) is planned. The trial will be double-blind. The participants to be enrolled will be ≥ 55 years old, generally healthy, have a normal PSA, and be free of significant chronic comorbid disease, especially severe symptoms of BPH.

The participants randomized will be scheduled for prostate biopsy following seven years of study treatment. The primary outcome is the presence or absence of prostate cancer as assessed by the end-of-study biopsy or prior to seven years on study.

It is projected that accrual will be completed in three years, with approximately 3,600 subjects (20%) randomized in the first year and approximately 7,200 subjects (40%) in each of years two and three. It follows that the last biopsy will be completed ten years following the beginning of enrollment.

The validity of this study depends on a number of CRITICAL ASSUMPTIONS related to the ability to know when a participant is not adherent, between arm comparability for the

participants who do not have a seven year biopsy, the mathematical form of the relationship of finasteride's effect on PSA levels, finasteride's effect on DRE and TRUS sensitivity, and the size of finasteride's effect in preventing BPH. (The CRITICAL ASSUMPTIONS are identified and discussed subsequently.) These CRITICAL ASSUMPTIONS are necessary because of finasteride's effect on the size of the prostate gland and particularly the tendency for finasteride to reduce PSA levels. The consequences of finasteride's effect on PSA are magnified by PSA's growing importance as a marker for prostate cancer incidence. In general terms, the intervention under study affects an important diagnostic test for the detection of the disease under study. These CRITICAL ASSUMPTIONS are necessary despite the design compromises made to accommodate finasteride's effect on PSA as described in the Background section of this protocol (Section 2.0).

The study is planned for a 5% two-sided test and will have 90% or greater power to detect a 25% difference between the arms in the proportion of prostate cancers following seven years of study treatment. This power computation is based on the following parameters: the non-adherence in the finasteride arm does not exceed 10%, the placebo arm finasteride use does not exceed 5%, and at least 60% of the participants have the seven year biopsy. The anticipated loss of participants is due to refusal, loss to follow-up, or death.

There will be no interim analysis of the primary outcome because the primary outcome will not be known until the end of the study. There will be close monitoring of the study with respect to safety, mortality, side-effects, conformity to the trial planning parameters, and conformity to the CRITICAL ASSUMPTIONS.

11.2 BIOPSY PRIOR TO SEVEN YEAR BIOPSY: A special procedure will be implemented to maximize the likelihood that the participants having biopsies prior to their scheduled end-of-study biopsy, for example as a result of positive digital rectal examination or elevated PSA, are comparable between the arms in both numbers and characteristics. Specifically, the finasteride arm PSA biopsy threshold will be adjusted based on experience with finasteride-induced downward shift in the PSA distribution so that approximately the same number of participants will be biopsied due to PSA elevations as in the placebo arm. This procedure is necessary because of the effect of finasteride on lowering PSA levels. If this procedure were not used, that is, if unadjusted PSA values were used as the threshold for biopsy in the finasteride arm, then participants in the placebo arm would have a greater probability of having a biopsy prior to the scheduled seven year biopsy, and therefore the placebo arm would likely have more cancers detected because of the greater number of biopsies.

CRITICAL ASSUMPTION: It is assumed that the finasteride-induced PSA change results in a simple downward shift in the PSA distribution and therefore generally preserves the original ranking of the affected participants.

If the preceding assumption does not hold then there is no basis for an assurance that the finasteride arm PSA threshold control procedure will result in comparable participants in each arm being biopsied prior to the seven year biopsy. The validity of this assumption can be tested by comparing between the arms the characteristics of the participants selected for biopsy based on the PSA threshold. The characteristics compared can include: baseline PSA, race, age, body dimensions, medication adherence rate, quality of life measurements, AUA symptom score, etc.

11.3 ADHERENCE/CONTAMINATION AND PSA: Participants in the finasteride arm who take less study drug than allotted could have a PSA level declared as "elevated" due to medication nonadherence since their PSA levels may not be as depressed as participants who are fully adherent. Similarly, it is theoretically possible for participants in the placebo arm who take finasteride (placebo arm contamination) to have finasteride-induced lowered PSA levels which masks a prostate cancer. A finasteride contamination effect is also

possible in the finasteride arm. Therefore the degree of medication adherence and contamination must be known when performing PSA assessments. The plan is to assess adherence/contamination prior to obtaining PSA specimens and to defer taking a PSA specimen in cases where there is evidence of nonadherence or contamination until there is sufficient adherence and lack of contamination. Thus, the participant is motivated to become adherent and not take open label finasteride. Also, meaningless PSA results are avoided. This strategy requires the following assumption, however:

CRITICAL ASSUMPTION: The procedures used to assess adherence in the individual participant at each visit where a PSA specimen is to be obtained are sufficiently sensitive and reliable to detect degrees of nonadherence affecting PSA level interpretation.

11.4 SEVEN YEAR BIOPSY: It is assumed that approximately 40% of the randomized participants will not have a prostate biopsy following seven years of study treatment and have not had a positive biopsy prior to seven years of treatment. Specifically, it is assumed there will be a 40% loss to biopsy based on the sum of 20% mortality, 15% lost to follow-up, and 5% biopsy refusals. The 20% mortality is based on an assumption that the median age at study entry will be 63 years, with the seven year U.S. (white) all-causes mortality for men that age assumed to be approximately 20%. The 15% lost to follow-up is based on experience with other prevention trials. The 5% biopsy refusal rate is based on the belief that participants who stay on the study drug for seven years will be motivated to find out whether or not they have prostate cancer.

CRITICAL ASSUMPTION: It is assumed that the factors affecting loss to biopsy will operate the same in both arms of the study so that the groups of participants who do not have biopsies (deaths, lost, refusal) will be comparable between the arms.

Conformity to the above assumption can be monitored by comparing between the arms the characteristics of the participants who do not have the seven year biopsy and the reason for not having the biopsy.

11.5 SENSITIVITY/SPECIFICITY OF DRE, TRUS, AND BIOPSY: It is known that finasteride generally reduces the prostate gland size, and therefore has the potential to affect the sensitivity and specificity of DRE and TRUS; furthermore, finasteride could affect the sensitivity of the prostate biopsy. The directions and degrees of finasteride's effect on these sensitivities and specificities are unknown at this time, and will be investigated as part of this study. These possible sensitivity and specificity effects, if they exists, would seriously compromise the validity of this trial since the design of this trial had to be based on the following assumption:

CRITICAL ASSUMPTION: Finasteride does not affect the sensitivity or specificity of the DRE or the TRUS, nor does finasteride affect the sensitivity of the prostate biopsy.

11.6 BPH AND TURP: It is theoretically possible that the incidence of benign prostatic hypertrophy (BPH) prior to the seven year biopsy in the finasteride arm will be less than in the placebo arm due to the potential of finasteride to prevent BPH. If there are relatively more BPH incident cases in the placebo arm then it is possible that there will be relatively more transurethral resections of the prostate (TURP) in the placebo arm, from which it follows that there could be relatively more incidental prostate cancers found in the placebo arm through the use of TURP. The implementation of a procedure for balancing the numbers of TURPs between the arms is not planned because it would interfere too much with standard urological practice. Thus, there is potential for a bias of unknown magnitude in favor of the finasteride arm with respect to prostate cancer incidence prior to the seven year biopsy. This potential bias will not be corrected by the seven year biopsy unless the sensitivity of the seven year biopsy is equal to or exceeds the sensitivity of the interim TURPs, but the relationship of these sensitivities is not known at this time. If this TURP bias exists then this trial will be anticonservative. It follows that the following assumption is necessary:

CRITICAL ASSUMPTION: It is assumed that any bias resulting from TURPs in BPH incident cases will be negligible.

11.7 ADHERENCE: A three month enrollment period during which each participant is to take study medication (in this case placebo) is part of the design. Following the enrollment period medication adherence will be assessed and only participants with sufficient adherence will be randomized. The degree of "placebo effect" will also be assessed and be a basis for exclusion from randomization.

For participants who have a prostate cancer at the end of the study it is assumed that the degree of placebo arm finasteride contamination, designated d0, will be approximately 0.05 (zero implies no contamination, one implies 100% contamination) and the degree of finasteride arm nonadherence, designated d1, will be approximately 0.10 (zero implies complete adherence and one implies 100% nonadherence). These degrees of contamination and adherence (d0 and d1) are used as follows. Let p0 and p1 be the true prostate cancer probabilities for the placebo arm and finasteride arms, respectively. The seven year prostate cancer probabilities adjusted for the assumed adherence and contamination are p0r = ((1- d0) x p0 + d0 x p1) and p1r = (d1 x p0 + (1-d1) x p1) for the placebo and finasteride arms, respectively.

11.8 PROBABILITY ASSUMPTIONS: The true probability of detectable prostate cancer in the placebo group at seven years following study entry (p0) is assumed to be in the neighborhood of 6% *(24,25)*.

The probability difference for seven years of treatment is defined as the difference of the true probability of prostate cancer at seven years in the finasteride arm minus the true probability of prostate cancer at seven years in the placebo arm, or p1 - p0 (NB: a negative difference implies a finasteride benefit). This difference is can be multiplied by 100 and divided by p0, that is 100 x (p1 - p0) / p0, to give the percent difference due to finasteride. The probability difference adjusted for the assumed degrees of placebo arm contamination and finasteride arm nonadherence is p1r - p0r and this difference is also can be used as the adjusted percent difference due to finasteride, or 100 x (p1r - p0r) / p0r.

11.9 PRIMARY ANALYSIS: The primary outcome analysis will consist of testing the coefficient of the arm indicator variable in a logistic regression model for the probability of prostate cancer. The logistic regression model will include covariates for all stratification factors except the Study Center. This analysis will include all subjects who have a biopsy at seven years plus the subjects who were found to have prostate cancer (histologically-proven) prior to seven years. The power computations which follow use standard formulas for computing the power when comparing proportions. The actual power of the trial is computed based on p0r and p1r, the probabilities adjusted for assumed degrees of contamination and nonadherence.

11.10 POWER: Based on 9,000 participants per arm, the graphs in Figure 4 illustrate actual power for an assumption of 60% of participants biopsied, true probability of prostate cancer in the placebo arm (p0) of 4% and 6%, unadjusted percent differences of 25% and 30%, and ranges for degrees of placebo arm contamination and finasteride arm nonadherence as described previously. If the desired actual power is 90% or above then the graphs in Figure 4 illustrate that this power is achievable provided: the unadjusted percent difference is 30%, the true probability of a positive biopsy in the placebo group (p0) is close to 6%, and the degree of placebo arm contamination and finasteride arm nonadherence do not become excessive. There is much less latitude for an unadjusted percent difference of 25%.

In particular, using the 60% biopsy rate, the power is 92.1% for an adjusted difference of 24.7% from a 6% placebo arm prostate cancer rate using a 5% placebo group contamination and a 14% finasteride arm nonadherence. This power computation is labeled in the fourth graph in Figure 4. These conditions are believed to be achievable if the trial is tightly controlled.

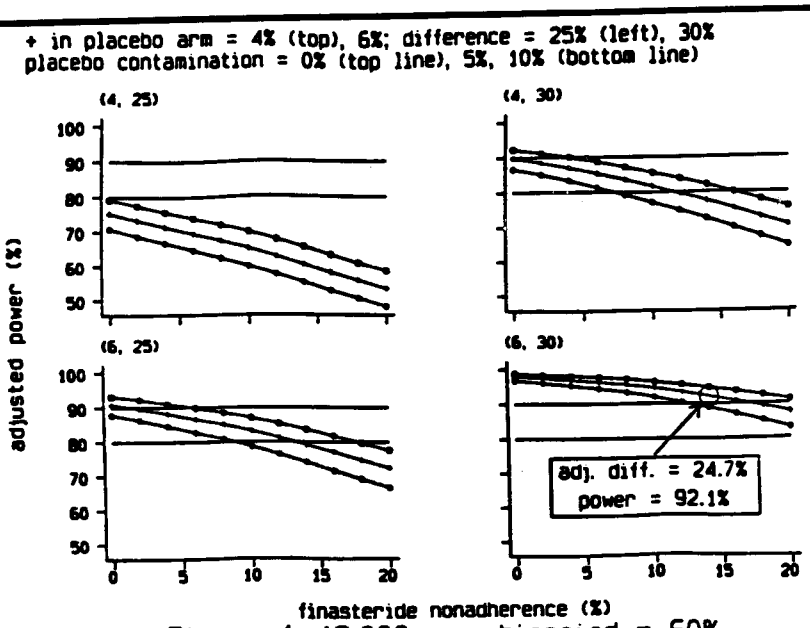


Figure 4: 18,000 men, biopsied = 60%

11.11 POWER FOR SIDE-EFFECTS AND ADVERSE EVENTS: The reported experience for one year of treatment with placebo (n=300) versus finasteride 5 mg (n=300) by the manufacturer includes the following:

	Finasteride	Placebo
decreased libido	4.7%	1.3%
ejaculatory disorder	4.4%	1.7%
impotence	3.4%	1.7%

The power using the first 1800 subjects per arm to detect differences in these measures (including a combined measure of sexual dysfunction) is shown below. The 1% one sided alpha level is used to permit five multiple comparisons at the 5% level.

side-effect percents		
placebo	finasteride	power
1	2	.50
	3	.97
	4	.99
2	4	.86
	5	.99
	6	.99
5	8	.90
	10	.99
10	13	.67
	15	.99

11.12 CARDIOVASCULAR DISEASE: Because cardiovascular disease is common among the men of age ≥ 55 (eligibility ages of the participants to be enrolled) the power will be high to detect even small differences between the arms with respect to cardiovascular disease

incidence and events. For example, if the incidence rate for coronary artery disease (CAD) for participants on this study is estimated to be 25 per 1000 per year then there could be as many as 1575 diagnoses of CAD in the placebo arm, that is, 17.5% of the placebo arm participants. The 0.05 one-sided power to detect a 10% higher incidence of CAD in the finasteride arm (1733 incident cases or 19.3%) would be 91.4%.

11.13 DATA AND SAFETY MONITORING: An external Data and Safety Monitoring Committee (DSMC) will review the safety, mortality, side-effects, adherence, and potential violation of the assumptions necessary for trial validity. The DSMC will review unblinded trial monitoring data every six months.

The Data and Safety Monitoring Committee (DSMC) will be an independent panel of urologists, statisticians, epidemiologists, and ethicists (approximately 10 total members). PCPT Study Investigators will be excluded from membership in this committee, but may participate in the review of blinded data as necessary.

The DSMC will be provided with detailed reports of all adverse events and deaths, including summaries of hospitalization discharges and deaths.

Side-effect data will be monitored more closely for the first cohort of 3600 subjects than for those who follow. The purpose of this monitoring will be to confirm previous finasteride studies which claimed minimal side-effects. Adherence data will be reviewed in order to provide the opportunity to implement additional adherence measures.

A monitoring system for detecting deviations from the CRITICAL ASSUMPTIONS will be active throughout the trial. This system will be used to generate data for DSMC review. Because of the fragility of this trial with respect to conformity to CRITICAL ASSUMPTIONS, and the resulting complexity of the monitoring tasks, no specific stopping rules are specified.

11.14 SECONDARY ANALYSES AND SECONDARY OBJECTIVES: Beyond the analysis of the primary outcome described above, the probability of prostate cancer at seven years will be modeled using standard methods for categorical data, with explanatory variables including age, race, family history, gland size, laboratory data, etc. The probability of side-effects will be modeled using information on adherence (and other covariates).

Objective 1.2 (finasteride's effect on stage and grade) will be analyzed by comparing between the arms the grade and stage distribution of the incident cases. Data will come from pathology review of biopsy specimens. Standard categorical data analysis methods will be used.

Objectives 1.3, 1.4, 1.5, and 1.7 (toxicity, side-effects, mortality, BPH, and quality of life) will be analyzed by comparing between the arms the rates of events and magnitudes of effects. The data will come from reports of events, participant interviews, and side-effect and quality of life questionnaires. Standard categorical data methods, including methods for ordered categorical data will be used.

Objective 1.6 (finasteride's effect on screening modality) will require detailed pathology data as well as an analysis of the data generated from the procedures used to adjust PSA levels. Should finasteride prove to be efficacious in preventing prostate cancer then it will be important to be able to recommend to practitioners methods for monitoring for prostate cancer in those taking finasteride. Additional data addressing this issue may become available from trials of the use of finasteride in BPH.

Objective 1.8 (association of dietary fat and an increased risk of prostate cancer) will be approached as detailed in Appendix 19.7, which outlines methods of data collection and analysis.

Objective 1.9 (cohort study of CAG repeat length) will be approached as detailed in Appendix 19.8.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

a. All participants registered on this study who undergo any procedure which yields prostate tissue for diagnosis (e.g., prostate biopsy, transurethral resection of the prostate, radical prostatectomy, open prostatectomy, fine needle aspiration of the prostate, or pelvic lymphadenectomy) must undergo centralized pathology review.

b. The materials from any of the above procedures are to be forwarded to the Core Laboratory within 30 days of the diagnostic/therapeutic procedure. Remaining tissue will be banked for future study.

Detailed procedures are found in Appendix Section 19.4.

13.0 REGISTRATION GUIDELINES

Enrollment and randomization procedures are specified in the Study Manual.

14.0 DATA SUBMISSION SCHEDULE

Detailed data submission procedures are found in the Study Manual.

15.0 SPECIAL INSTRUCTIONS

15.1 Central Laboratory Facility (CLF): All PSA/DHT/Cholesterol determinations will be performed by Endocrine Sciences. Additional sera will be banked for future study. Detailed procedures are found in the Study Manual.

15.2 The Serum and Tissue Utilization Subcommittee will oversee the use of the serum and tissue banks. Detailed procedures are found in the Study Manual.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Participants (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Participants (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the participant to whom drug is dispensed, the date(s) and quantity of drug dispensed to the participant, and the date(s) and quantity of drug returned by the participant; participants should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

Adverse Experiences

Any unexpected or serious adverse experience, if deemed drug related, must be reported within 24 hours to the Southwest Oncology Group Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Depending on the nature of the reaction, the ADR representative will advise further. See guidelines on next page. All deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the participant received to make therapeutic decisions, the code for that particular participant can be broken by telephoning the central unblinding number (see Study Manual for more details).

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Southwest Oncology Group Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRs)/ADVERSE EVENTS (AEs) OCCURRING WITH FINASTERIDE ON **SWOG-9217**

WITHIN 24 HOURS OF NOTIFICATION OF THE REACTION

CALL THE OPERATIONS OFFICE AT 210/677-8808

WITHIN 10 DAYS, SEND TO THE OPERATIONS OFFICE

1) **A COPY OF THE ADR REPORTING FORM**
2) **IRB NOTIFICATION DOCUMENTATION**
3) **COPIES OF ALL DATA RECORDS**

All Grades 3 - 5 Unknown Reactions and Grades 4 - 5 Known Reactions according to the Southwest Oncology Group Toxicity Criteria must be reported as ADRs/AEs. All hospital discharge summaries and death certificates will be submitted for evaluation.

For grading reaction, see Southwest Oncology Group Toxicity Criteria, Section 19.0. Please do NOT use the NCI Common Toxicity Criteria version 2.X for toxicity or adverse event reporting.

The ADR report should be documented on the Southwest Oncology Group ADR Form and mailed to the following address:

ATTN: ADR Program
Southwest Oncology Group
Operations Office
14980 Omicron Drive
San Antonio, Texas 78245-3217

A list of all known toxicities can be found in either the Drug Information, Background or Informed Consent Form of the protocol.

New diagnoses of cancer, including prostate cancer, in PCPT participants need not be reported as adverse events. However, all diagnosis of cancer must be reported as assessment data in accordance with Section 9.0 and the Study Manual.

Reactions judged definitely not to be treatment related should not be reported. **However, a report shall be submitted if there is only a reasonable suspicion of drug effect.**

Copies of reports of all Grades 3 - 5 Unknown Reactions will be forwarded from the Operations Office to the FDA (using the guidelines provided in the Code of Federal Regulations 21 CFR 312.32), Dr. Ian M. Thompson, Jr., M.D., DCPC and Merck Research Laboratory.

Specific Adverse Event Reporting Guidelines for PCPT
End-of-study Prostate Biopsies

· Adverse events *related to biopsy* that should be reported:

1. Bleeding requiring either hospitalization or transfusion
2. Infection requiring antibiotic therapy
3. Any hospital admission (include diagnosis and outcome in report)
4. Death

· If any other biopsy-related event occurs that seems to meet the requirement for reporting according to the protocol adverse event guidelines, call the AE Specialist in the Operations Office (210-677-8808) to discuss.

17.0 BIBLIOGRAPHY

1. Boring CC, Squires TS, Tong T. Cancer Statistics, 1992. CA 42:19-38, 1992.

2. Seidman H, Mushinski MH, Gelb SK, Silverberg E. Probabilities of eventually developing or dying of cancer - United States, 1985. CA 35:36, 1985.

3. Catalona WJ, Smith D, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. NEJM 324:1156, 1991.

4. Chodak GW, Thompson IM, Gerber GS, et al. Results from two prostate cancer screening programs. JAMA (in press).

5. Mishina T, Watanabe H, Araki H, et al. Epidemiological study of prostatic cancer by matched-pair analysis. The Prostate 6:423, 1985.

6. Pollard M, Luckert PH. The inhibitory effect of 4-hydroxyphenyl retinamide (4HPR) on metastasis of prostate adenocarcinoma-III cells in Lobund-Wistar rats. Cancer Letters 59:159, 1991.

7. Kaul L, Hashmat MY, Kovi J, et al. The role of diet in prostate cancer. Nutr Cancer 9:123-8, 1987.

8. Willett WC, Polk BF, Underwood BA, et al. Relation of serum vitamins A and E and carotenoids to the risk of cancer. NEJM 310:430, 1984.

9. Costa A, Malone W, Perloff M, et al. Tolerability of the synthetic retinoid Fenretinide (4HPR). Exp J Cancer Clin Oncol 25:305, 1989.

10. Imperato-McGinley J, Guerrero L, Gautier T, et al. Steroid 5-alpha reductase deficiency in man: An inherited form of male pseudohermaphroditism. Science 186:1212, 1974.

11. Walsh PC, Madden JD, Harrod MJ, et al. Familial incomplete male pseudohermaphroditism, Type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. NEJM 291:944, 1974.

12. Ross RK, Bernstein L, Judd H, et al. Serum testosterone levels in young African-American and Caucasian men. J National Cancer Institute 76:45, 1976.

13. Bruun E, Grandsen H, Nielsen K, et al. Dihydrotestosterone measured in core biopsies from prostatic tissues. Am J Clin Oncol Suppl 2:S27, 1988.

14. Habib GK, Bissas A, Neill WA, et al. Flow cytometric analysis of cellular DNA in human prostate cancer: relationship to 5 alpha-reductase activity of the tissue. Urol Res 17:239, 1989.

15. Kadoham N, Karr JP, Murphy GP, et al. Selective inhibition of prostatic tumor 5 alpha reductase by a 5-methyl-4-aza-steroid. Cancer Res 44:947, 1984.

16. Petrow V, Padilla GM, Mukherji S, et al. Endocrine dependence of prostatic cancer upon dihydrotestosterone and not upon testosterone. J Pharm Pharmacol 36:352, 1984.

17. Muir C, Waterhous J, Mack T, et al. Cancer Incidence in five continents. Volume V, IARC, Lyon, 1987.

18. SEER: Cancer incidence and mortality in the United States, 1973-1981. Bethesda, MD. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute. 1984.

19. Ross RK, Bernstein L, Lobo RA, et al. Evidence for reduced 5 alpha-reductase activity in Japanese compared to U.S. Caucasian and African-American males: Implications for prostate cancer risk. Lancet 339:887, 1992. (April 11, 1992)

20. Bologna M, Muzi P, Biordi L, et al. Antiandrogens and 5-alpha reductase inhibition of the proliferation rate in PC3 and DU145 human prostatic cancer cell lines. Curr Therapeutic Research 51:799, 1992.

21. Gormley GJ, Stoner E, et al. The effect of finasteride in men with benign prostatic hyperplasia. NEJM. In Press.

22. Brawer MK, Chetner MP, Beatie J, et al. Screening for prostatic carcinoma with prostate specific antigen. J Urology 147:841, 1992.

23. Cater HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 267:2215, 1992.

24. Cooner WH, Mosley BR, Rutherford CL, et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J Urology 143:1146, 1990.

25. Corder EH, Chute CC, Guess HA, et al. Prostate cancer in Rochester, Minnesota: Incidence 1935 to 1989. Abstract accepted for oral presentation at the Society for Epidemiologic Research Annual Meeting, June 1992.

26. Guess HA, Heyse JA, Gormley GG. The effect of finasteride on prostate specific antigen in men with benign prostatic hyperplasia. The Prostate (manuscript submitted for publication)

27. Whitmore WF, Warner JA, Thompson IM. Expectant management of localized prostatic cancer. Cancer 67:1091, 1991.

28. Johansson JE, Adami HO, Andersson SO, et al. High 10-year survival rate in patients with early, untreated prostatic cancer. JAMA 267:2191, 1992.

29. Aaronson NK, Bakker W, Stewart AL, et al. Multidimensional approach to the measurement of quality of life in lung cancer clinical trials. In Monograph series of the European Organization for Research and Treatment of Cancer (Aaronson NK, Beckmann JH, eds), vol 17. New York: Raven Press, pp 63-82, 1987.

30. Moinpour et al. Quality of Life in Cancer Clinical Trials: Review and Recommendations. J National Cancer Institute 81:485-495, 1989.

31. Quality of Life in Current Oncology Practice and Research. Special Issue of Oncology 4(5), 1990. Also as: Tchekmedyian NS, Celia DF (Eds). Quality of Life in Oncology Practice and Research. Williston Park, NJ: Dominus Pub., 1991.

32. Spilker B (Ed). Quality of Life Assessments in Clinical Trials. New York: Raven Press, 1990.

33. Osoba D (Ed). Effeect of Cancer on Quality of Life. Boca Raton, FL: CRC Press, 1991.

34. Nayfield SG, Ganz PA, Moinpour CM, et al. Report from a National Cancer Institute workshop on quality of life research in cancer clinical trials. Quality of Life Research 1:203-210, 1992.

35. Stewart AL, Ware JE Jr. Measuring Functioning and Well-Being. The Medical Outcomes Study Approach. Duram and London: Duke University Press, 1992.

36. Martin DP, Gilson BS, Bergner M, et al: The Sickness Impact Profile: Potential use of a health status instrument for physician training. J Med Educ 51:942-944, 1976.

37. Brody DS: Physician recognition of behavioral, psychosocial, and social aspects of medical care. Arch Intern Med 140:1286-1289, 1980.

38. Wartman SA, Morlock LL, Malitz FE, et al: Impact of divergent evaluations by physicians and patients of patient's complaints. Public Health Rep 98:141-145, 1983.

39. Nelson E, Conger B, Douglass R, et al: Functional health status levels of primary care patients. JAMA 249:3331-3338, 1983.

40. Maguire P: Using measures of psychological impact of disease to inform clinical practice. In Proceedings of the International Workshop on Quality of Life Assessment and Cancer Treatment (Ventafridda V, van Dam FSAM, Yancik R, et al, eds). Amsterdam: Excerpta Medica, 1986, pp 119-126.

41. Ware JE Jr, Brock RH, Williams RN, et al: Conceptualization and measurement of health for adults in the Health Insurance Study. In Model of Health and Methodology, vol I. DHEW Publ No. R-1987/I. Santa Monica, CA: Rand Corp, 1980.

42. Stewart Al, Hays RD, Ware JE Jr: The MOS Short-form General Health Survey. Reliability and validity in a patient population. Med Care 26:724-735, 1988.

43. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA 262:907-913, 1989.

44. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short Form Health Survey (SF-36), I. Conceptual framework and item selection. Med Care 30:473-481, 1992.

45. O'Leary MP, Barry MJ, Fowler FJ Jr. Hard measures of subjective outcomes: validating symptoms indexes in urology. J Urology 148:1546-1548, 1992.

46. Barry MJ, Fowler FJ Jr., O'Leary MP, et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. J Urology 148:1549-1557, 1992.

47. Barry MJ, Fowler FJ Jr., O'Leary MP, et al. Correlation of the American Urological Association Symptom Index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment Program symptom indexes. J Urology 148:1558-1563, 1992.

48. Eisner E, Tobin E. What should we tell men about prostate cancer? Focus group research to help develop a communications strategy on prostate cancer for older men. Bethesda, MD: Office of Cancer Communications, National Cancer Institute, October, 1992.

49. Hodge KK, McNeal JE, Terris MK, et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urology 142:71, 1989.

50. National Cholesterol Education Program. Highlights of the report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 88-2926, November, 1987.

51. Merck Sharp & Dohme. Proscar (Finasteride) package insert. May, 1992.

52. Crawford ED, DeAntoni EP, Stone NN, Bunn DS for the Prostate Cancer Education Council. Prostate Cancer Awareness Week, 1989-1992: lessons in the early detection of prostate cancer. ASCO 12:245(#769), 1993.

53. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Liber MM. Serum prostate specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. JAMA 270(7):860-864, 1993.

54. Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60064. IMX PSA kit insert, August 1991.

18.0 MASTER FORMS SET

Forms and procedures are contained in the Study Manual.

A copy of the Model Informed Consent document is enclosed and must be reviewed and approved by the institutional IRB before placing a participant on study.

A copy of the Model Informed Consent document for the Participant Database is also enclosed and must be reviewed and approved by the institutional IRB before being presented to participants.

A copy of the Model Informed Consent document for the White Blood Cell and Plasma Collection Procedures is also enclosed (in **Section 19.9**) and must be reviewed and approved by the institutional IRB before being presented to the participants.

A copy of the Model Informed Consent document for the Extended Follow-Up is also enclosed (in **Section 19.10**) and must be reviewed and approved by the Institutional IRB before being presented to the participants.

This model informed consent form has been reviewed by the DCPC/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Sections of this document which are in bold type should always be tried to be used in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they should be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a participant may be registered to this study.

CONSENT FORM AND INFORMATION ABOUT

SWOG-9217, Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III

TO BE CONDUCTED AT

_____

_____

_____

I. **You are invited to take part in this research study because you are a male of age 55 or older who has never been diagnosed with prostate cancer. You are being asked to participate in this research to determine if the medication, finasteride, can prevent prostate cancer.**

Prostate cancer is the most common cancer in older men, but only approximately one man in ten in your age group will develop prostate cancer during their life. The goal of this study is to determine if men using finasteride have a lower risk of developing prostate cancer.

We also want to find out what the quality of life for participants is according to the type of treatment they receive. It is very important to have your view about how you have been feeling during your treatment. This is especially important because you are healthy and this treatment is being used for possible prevention of cancer rather than as a treatment for a disease. By completing a questionnaire on a regularly scheduled basis, you will help describe the effect of this treatment on your quality of life.

We would also like to store your blood and tissue for possible use in future research studies. None of these would be of benefit to you, but could help us learn about other ways to prevent cancer. For this purpose, an extra 14 cc (about 3 teaspoons) will be drawn for future research purposes. *(4/14/95)*

Some research may require no identification of blood or tissue, so there would be no risk to you. We will keep a file that will allow identification of samples. If further projects are planned that require use of identifiable samples, you will be contacted and your consent would be necessary to do such research. (If you do not want to be contacted for future studies you can check a box at the end of this form.) *(4/14/95)*

As part of the ongoing scientific and biotechnological activities of the Southwest Oncology Group and its agents, these blood samples and any tissue specimens will be preserved and used for research and development purposes. As a result of these biotechnological activities, an economic benefit may be derived directly or indirectly by the Southwest Oncology Group, individual researchers, and others engaged in these activities. By signing this consent form, you authorize the preservation and use of these blood samples and any tissue specimens taken from you. *(4/14/95)*

For the individual participants in this study, it is not known if the risks will outweigh the benefits. The major potential benefit for the participants receiving finasteride is the prevention of prostate cancer if the study shows finasteride may or will have that effect. *(2/5/96)* **Other potential benefits include shrinking of an enlarged prostate gland with resultant increase in urinary flow rate.**

II. If you decide to take part in this study, you will first undergo a digital rectal examination (in which the doctor feels the surface of your prostate with a gloved finger, feeling for irregularities which may be suspicious for cancer). You will also have a blood test (Prostate Specific Antigen or PSA) done which can be elevated in men with prostate cancer. If both of these tests are normal, your treatment will be decided by a process called randomization (similar to flipping a coin). Of the 18,000 men to be enrolled on this study, 9,000 will receive finasteride and 9,000 will receive a placebo (a tablet containing no medication). At some point during their participation in the study, every participant will receive placebo tablets for a period of time. You will receive your treatment as an outpatient. Your treatment (finasteride or placebo tablet) will be taken orally (by mouth) every day. You will not be informed which tablet you have been receiving until the end of the study, except in the case of a medical emergency.

While you are on this study, you will be seen initially at three months. At that time, you will be asked about any side effects you may be having from the tablet. If you are not experiencing difficulties, are taking the tablets on a regular basis, and desire to continue the study you will receive additional tablets. You will then return every six months. Once each year, your clinician will perform an examination of the prostate (digital rectal examination) as well as a blood test (prostate specific antigen) to look for evidence of prostate cancer. If the digital examination of the prostate suggests the presence of prostate cancer, your physician may recommend a prostate biopsy. *(2/5/96)*

During follow-up, if your prostate specific antigen (PSA) blood test becomes elevated, prostate cancer may be the cause. Your physician may recommend a prostate biopsy. Because the study drug, finasteride, directly affects the PSA level, the group receiving the study drug will have a different PSA level that prompts the recommendation for biopsy than that in participants who are not receiving finasteride. *(12/30/96)* For this reason, your blood test will be performed at a central laboratory and the results will be reported to your physician as "elevated" or "normal". By doing so, it will generally make your risk of needing a prostate biopsy equal, regardless of which treatment you receive.

Biopsy of the prostate involves the placement of a sound-wave device into the rectum immediately next to the prostate gland. Using this sound-wave device to look at the prostate as well as a guide, several pieces of tissue are removed from the gland. This can be somewhat uncomfortable and can cause bleeding in the urine or rectum or blood-tinged ejaculate (body fluid released by the prostate during sexual intercourse). There is also a risk of temporary inability to urinate or infection. If prostate cancer is detected, you will stop the study drug and will be treated in accordance with your wishes based upon recommendations made by your physician. *(2/5/96)*

It may be possible during the conduct of this study that a prostate biopsy is required of a group of individuals participating in the study. This may be required due to differences in the PSA blood test in the two groups.

In addition, you will also be monitored for your risk of heart disease. If you have abnormal cholesterol levels based on the blood specimen obtained at enrollment or are otherwise at high risk for heart disease, you will be referred to a doctor for evaluation and possible treatment of this problem. The purpose of this monitoring is to allow the study investigators to adequately interpret heart disease related events which occur during this study. *(2/5/96)*

You will be expected to continue on the study for seven years. *(4/14/95)* At the end of the study, a prostate biopsy will be required. The tissue removed from your prostate at any time during the study will be sent to a laboratory for testing and storage.

It is anticipated that early prostate tumors may be found during this study which otherwise would not have been found. However, it is also possible that tumors which do not need treatment may be found. At this time it is difficult to tell the difference between these types of tumors and it is therefore possible that you may receive unnecessary treatment which involves a significant risk of side-effects. *(2/5/96)* The treatment that you will receive if prostate cancer is found during the study will be decided by you and your doctor.

There are circumstances under which your doctor might be required to discontinue your tablets whether you agree or not. These circumstances include: the side effects of the treatment are placing you at undue risk; new information about the drug becomes available and this information suggests the drugs will be ineffective or unsafe for you.

The tablets are provided free of charge, as are the analyses of the PSA blood tests and the biopsy at the end of the seven years. Blood will be drawn for a cholesterol screening test at the first visit. This test will be completed and results provided free of charge only after you are randomized for the study. All clinic charges associated with the physical exams, drawing blood, and the rectal exams must be paid for by you or your insurance company. If cancer or other prostate diseases are discovered during the regular exams, then you will be referred to a doctor for care. Costs for diagnosis and treatment of prostate problems, prostate cancer, or other medical conditions during the seven years of the study are also paid for by you or your health insurance, just as they would be if you were not part of this study. These examinations are not a substitute for regular health check-ups such as an annual physical examination by your own doctor.

Finasteride is an approved drug for otherwise healthy men with a condition called "benign prostatic hyperplasia". It has been tested in more than 3,000 men and serious side-effects have not been evident.

III. **Side effects some people have had after receiving finasteride therapy are listed as follows according to how often these side effects have been reported: impotence (failure to have or maintain an erection) (fewer than 4 out of 100 men), decreased sex drive (fewer than 4 out of 100 men), and decrease in the amount of semen released during intercourse (fewer than 3 out of 100 men). A very small number of reports have been received listing a severe allergic reaction as a side-effect of finasteride. This reaction may cause swelling of the lips, skin rash and itching. Although allergic reactions to this drug have been mild, this type of reaction may also cause swelling of the air passages and difficulty breathing. Reports have also been received listing breast enlargement and tenderness as a side-effect.** *(12/30/96)*

Although finasteride has been associated with the side effects described above, other side effects may occur which were not seen before. The side effects are usually temporary and stop when the drug is stopped. In some cases side-effects went away even while continuing to take finasteride.

If you are sexually active and your sexual partner is capable of bearing children, we strongly recommend that you use an effective method of birth regulation to avoid fathering a child during the course of this study. If your sexual partner is currently pregnant we strongly recommend that you use a condom to avoid exposing your sexual partner to your semen during the pregnancy. The amount of finasteride that could be absorbed from semen by a woman is unknown. There is a possibility that finasteride can harm a developing male fetus.

Additionally, crushed finasteride tablets should not be handled by a woman who is or may become pregnant because of the possibility of absorbing the drug through the skin. Because you will not know whether or not you are receiving finasteride, you are asked to refrain from donating blood or blood products while you are taking the study drug. This precaution is also to prevent exposure to finasteride by a woman who is or may become pregnant.

There is no known treatment for preventing prostate cancer. *(2/5/96)*

IV. No commitment is made to provide free medical care or compensation in the event of injury or illness resulting from participation in this study. Continuing medical care and/or hospitalization will not be provided free of charge but must be paid for in the same way your regular medical care is paid. We cannot pay you to take part in this study.

V. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration, a qualified representative of the drug manufacturer, and the Southwest Oncology Group. When we publish the information we learn from this study in a medical journal, you will not be identified by name. Your medical records for this study will be sent by facsimile transmission (FAX machine) directly into a central computer. It is possible (although unlikely) that your records could be sent to the wrong machine in error.

VI. Whether or not you take part in this study will not affect your future relations with your doctors (there will be no loss of benefit or change in attitude) or _____ (hospital name). If you decide to take part, you are free to stop whenever you want to.

VII. You have the right to refuse to participate in this research study (and receive any treatment recommended by your physician) if you so desire without any fear of penalty or loss of benefits. In addition, you may refuse to continue on this study, at any time after the start of therapy, without fear of prejudice to additional treatment. If you withdraw from the treatment part of this study, we would like to continue to follow you and, unless you object, collect information from your medical records. *(4/14/95)* By signing this form, you recognize that you have received a copy of it, and your signature indicates that you have volunteered to participate in the study after having read the information provided to you.

VIII. The doctor(s) involved with your care can answer any questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

	Office	Home
Dr.		
Dr.		
Dr.		

You can also call the Institutional Review Board (#_____) if you have any questions, comments or concerns about the study or your rights as a research participant.

IX. We will give you a copy of this form to keep.

X. You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer. *(4/14/95)*

_____ _____
Date Signature of Participant

_____ _____
Signature of Witness Signature of Investigator

_____
Time

❑ I do not wish to be contacted for future studies on my stored blood fluid or tissue. *(4/14/95)*

This model informed consent form has been reviewed by the DCPC/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Sections of this document which are in bold type should always be tried to be used in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they should be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a participant may be registered to this study.

CONSENT FORM AND INFORMATION ABOUT

SWOG-9217, Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III
PARTICIPANT DATABASE PROJECT

TO BE CONDUCTED AT

_____

_____

_____

The Prostate Cancer Prevention Trial (PCPT) is creating a centralized database of participant names and addresses. This database will be used to create address labels in order to send study-related materials and information directly to you from the Southwest Oncology Group Statistical Center and/or Operations Office. The centralized database will facilitate quicker mailing of these materials to you since they will not have to be routed through your study site.

Only the PCPT staff at [name of participant's Study Site], the Southwest Oncology Group Statistical Center in Seattle, Washington and the Southwest Oncology Group Operations Office in San Antonio, Texas will have access to your name and address exclusively for the purpose of study-wide mailings. Your address form will be sent by facsimile transmission (fax machine) directly into a central computer. It is possible (although unlikely) that your records could be sent to the wrong machine in error. Your address information will not be rented, sold or made available to any person and/or group outside the Prostate Cancer Prevention Trial.

You do not have to provide your name and address as part of your involvement with the PCPT. If you do not provide your name and address, study-related materials and information will continue to be distributed to you by your Study Site.

All of your study records will be kept confidential to the extent required by law. When we publish the information we learn from this study, you will not be identified by name.

Participant Statement

I have read this permission form and understand its purpose. I have contacted my PCPT Study Site to discuss any questions I have, or to discuss any parts of this permission I do not understand. I understand that I may ask further questions at any time. I understand that I may remove my name and address from the participant database at any time for any reason.

_____ _____
Signature of Participant Date

_____ _____
Signature of Witness Signature of Investigator

_____
Time

19.0 APPENDIX

19.1 This section contains the Southwest Oncology Group Toxicity Criteria.

19.2 Staging Criteria

19.3 Risk Factors for Coronary Heart Disease

19.4 Pathology Review Procedures

19.5 DRE, TRUS and Biopsy Procedures

19.6 Participants

19.7 Diet Ancillary Study

19.8 CAG Repeat Length Ancillary Study

19.9 White Blood Cell and Plasma Collection Procedures

19.10 Extended Follow-Up

SOUTHWEST ONCOLOGY GROUP TOXICITY CRITERIA

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period.
2. Toxicity grade = 5 if that toxicity caused or contributed to the death of the patient.
3. Do not code if the symptoms are certainly or most likely due to disease or other non-treatment cause.
4. If patient at baseline has Grade 1 or greater, do not code unless patient worsens due to toxicity. If there is worsening, code the level the patient increases to -- do NOT adjust for baseline.
5. Code all toxicities that apply, e.g., for a patient with pneumonitis, code pneumonitis as well as any pulmonary function codes which apply.
6. NCI codes for infection, pulmonary, neuro-sensory, neuro-cortical, neuro-cerebellar, neuro-constipation and skin will be calculated at the Statistical Center from the Southwest Oncology Group codes.
7. Note that for some toxicities certain grades are not defined and may not be coded.
8. Granulocytes/Bands refers to segmented neutrophils plus bands.

		GRADE				
Codes	Toxicity	0	1	2	3	4
	HEMATOLOGIC					
HE0	WBC	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
HE1	PLT	≥ LLN	75.0 - < LLN	50.0 - 74.9	25.0 - 49.9	< 25.0
HE2	Hgb	≥ LLN	10.0 - < LLN	8.0 - 9.9	6.5 - 7.9	< 6.5
HE3	Granulocytes/ Bands	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
HE4	Lymphocytes	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
HE9	Hematologic- Other (specify)		mild	moderate	severe	life-threatening
	CARDIAC					
CA0	Cardiac- Dysrhythmia	none	asymptomatic, transient requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension or ventricular tachycardia, or fibrillation
CA1	Cardiac- EF/CHF	none	asymptomatic, decline of resting ejection fraction by ≤ 20% of baseline value	asymptomatic, decline of resting ejection fraction by > 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
CA2	Cardiac- Ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
CA3	Cardiac- Pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
CA9	Cardiac- Other (specify)	mild	moderate	severe	life-threatening	
	CIRCULATORY					
CI0	Hypertension	none or no change	asymptomatic, transient increase by > 20mm Hg (D) or to > 150/100 if previously WNL. No treatment required	recurrent or persistent increase by > 20mm Hg (D) or to > 150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
CI1	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization; or syncope	requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for > 48 hrs after stopping the agent, or shock

Codes	Toxicity	GRADE 0	1	2	3	4
CI2	Phlebitis/ Thrombosis/ Embolism	none		superficial phlebitis (not local)	Deep vein thrombosis	major event (cerebral, hepatic, pulmonary, other infarction) or pulmonary embolism
CI3	Edema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca
CI4	Veno-Occlusive Disease	none			yes	
CI9	Circulatory Other (specify)		mild	moderate	severe	life-threatening
	CLOTTING					
CL0	Fibrinogen	≥ LLN	0.99 - 0.75 x LLN	0.74 - 0.50 x LLN	0.49 - 0.25 x LLN	≤ 0.24 x LLN
CL1	Prothrombin Time	≤ ULN	1.01 - 1.25 x ULN	1.26 - 1.50 x ULN	1.51 - 2.00 x ULN	> 2.00 x ULN
CL2	Partial Thromboplastin Time	≤ ULN	1.01 - 1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3.00 x ULN	> 3.00 x ULN
CL9	Clotting - Other (specify)		mild	moderate	severe	life-threatening
	DERMATOLOGIC					
SK0	Local	none	pain, erythema or itching	pain and swelling, with inflammation or phlebitis	ulceration or necrosis	plastic surgery indicated
SK1	Skin Rash/Urticaria	none	asymptomatic scattered macular or papular eruption	scattered eruption with pruritus or other symptoms	generalized symptomatic eruption	exfoliative dermatitis
		(also code Skin Ulceration or Skin Necrosis if applicable)				
DE6	Pruritus	none	mild and localized; relieved spontaneously or by local measures	intense or widespread; relieved spontaneously or by systemic measures	intense or widespread; incompletely relieved any measure	
SK2	Blistering	none	asymptomatic eruption	limited eruption, symptomatic	generalized symptomatic eruption	
		(also code Desquamation, Skin Ulceration or Skin Necrosis if applicable)				
SK3	Erythema	none	asymptomatic	erythema with pruritus or tenderness		
SK4	Erythema in RT Field	(same definition as Erythema)				
SK5	Desquamation	normal	peeling, dry desquamation	patchy moist desquamation	confluent moist desquamation other than skin folds	
		(also code Skin Ulceration or Skin Necrosis if applicable)				
SK6	Desquamation in RT Field	(same definition as Desquamation)				
SK7	Skin Necrosis (non-local)	none				yes
SK8	Skin Ulceration (non-local)	none				yes but ≤ 2 weeks
SK9	Chronic Skin Change	none		telangiectatic changes or atrophy	fibrosis, contractures or scarring	non-healing ulcers > 2 weeks
DE0	Pigmentation Changes	none	mild	pronounced		
DE1	Photosensitivity	normal		yes		
		(also code Erythema, Blistering or Desquamation if applicable)				
DE2	Dry Skin	normal	controlled with emollients	not controlled with emollients		
DE3	Hand-foot Syndrome	no	-	yes		
		(also grade appropriate dermatologic phenomena)				
DE4	Granuloma	no	-	yes		
		(also grade Pain if it applies)				

Codes	Toxicity	GRADE 0	1	2	3	4
DE5	Skin Yellowing	none	present on close exam	prominent (seen at a distance)		
DE9	Dermatologic- Other (specify)		mild	moderate	severe	life-threatening
	ENDOCRINE					
EN0	Impotence/ Libido	normal	decrease in normal function		absence of function	
EN1	Sterility				yes	
EN2	Gynecomastia	normal	mild	pronounced or painful		
EN3	Hot flashes	none	mild or < 1/day	moderate and ≥ 1/day	frequent and interferes with normal function	
EN4	Menses: At time off study, did pt. experience -	normal menses throughout	occasionally irregular or lengthened interval, but continuing	very irregular, but continuing	amenorrhea, no menses for at least 6 mo	
EN5	Cushingoid	normal	mild	pronounced		
EN6	Erectile Impotence	nothing wrong	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	severe (no erections)	
EN9	Endocrine- Other (specify)		mild	moderate	severe	life-threatening
	EYE					
EY0	Conjunc-tivitis/ Keratitis	none	erythema or chemosis not requiring steroids or antibiotics	requires treatment with steroids or antibiotics (also code Vision if applicable)	corneal ulceration or visible opacification	
EY1	Dry eye	normal		requires artificial tears		requires enucleation
EY2	Glaucoma	no change			yes	
EY9	Eye- Other (specify)		mild	moderate	severe	life-threatening
	FLU-LIKE SYMPTOMS					
FL0	Fever in Absence of Infection	none	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C > 104.0°F for less than 24 hours	> 40.0° C (104.0°F) for more than 24 hours or fever accompanied by hypotension
FL1	Chills	none	mild or brief	pronounced and prolonged		
FL2	Myalgia/ Arthralgia	normal	mild	decrease in ability to move	disabled	
FL3	Sweats	normal	mild and occasional	frequent or drenching		
FL4	Facial Flushing	normal	yes			
FL9	Other Flu-Like Symptoms (specify)		mild	moderate	severe	life-threatening
	GASTROINTESTINAL					
GI0	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	
GI1	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or re-quiring parent-eral support
GI2	Diarrhea	none	increase of 2 - 3 stools/day over pretreatment	increase of 4 - 6 stools/day, or nocturnal stools or mod-erate cramping	increase of 7 - 9 stools/ day, or incon-tinence, or severe cramping	increase of ≥ 10 stools/ day, grossly bloody diarrhea or need for parenteral support

		GRADE				
Codes	Toxicity	0	1	2	3	4
GI3	Constipation	none	stool softener required	laxatives required	obstipation with enema, manual or surgical evacuation required	
GI4	Ileus	no			yes, < 96 hrs	yes, ≥ 96 hrs
GI8	Anal Incontinence	no	resolves without treatment (< 1 wk); self-limited illness	controlled by diet or generic antidiarrheal	medically uncontrollable or controlled by surgery	
GI5	Gastritis/ Ulcer	no	antacid	requires vigorous medical management or non-surgical treatment	uncontrolled by medical management; requires surgery for GI ulceration	perforation or bleeding
GA0	Pancreatitis	no			inflammatory response confined to pancreas; self-limited	shock; pancreatic hemorrhage or necrosis;
GI6	Small Bowel Obstruction	no		intermittent, no intervention	illness requires intervention	chronic illness requires operation
GI7	Intestinal Fistula	no			yes	
GI9	GI - Other (specify)		mild	moderate	severe	life-threatening
	HEMORRHAGE					
HM0	Hemorrhage (clinical)	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, > 4 units transfusion per episode
HM2	Epistaxis	none	self-limited, controlled by conservative measures		cauterization, artery ligation or packing of posterior nasal cavity; requires hospitalization	
HM1	Rectal Bleeding	none		intermittent, no steroids	requires steroids	requires transfusion (code hemorrhage also)
HM3	Vaginal bleeding	normal	prolonged, increased frequency or profuse but self-limited; no or minimal local tx required	medical therapy required	uterine curettage	requires transfusion (code hemorrhage also)
	IMMUNOLOGICAL					
IM0	Allergy (also code rash if it applies)	none	transient rash, drug fever < 38° C, 100.4°F	urticaria, drug fever ≥ 38° C, 100.4°F, mild bronchospasm	serum sickness, bronchospasm, requires parenteral meds	anaphylaxis
IM1	Immunosensitivity Reaction	none	(definitions will be agent specific)			
IM2	Acute GVHD	none	I	II	III	IV
IM9	Immuno - Other (specify)		mild	moderate	severe	life-threatening
	INFECTION					
IN0	Other Infection (specify site)	none	no active treatment (e.g., viral syndromes)	PO antibiotics	IV antibiotic or antifungal or hospitalization	life-threatening e.g., septic shock
IN1	Respiratory Infection	(Same definitions as Other Infection)				
IN2	Urinary tract Infection	(Same definitions as Other Infection)				

Codes	Toxicity	GRADE 0	1	2	3	4
IN3	Wound Infection	no		PO antibiotics	IV antibiotic or antifungal or surgical intervention	life-threatening e.g., septic shock
IN5	Infection at Catheter Site	no		Local care and PO antibiotics; local infection	Febrile illness; IV antibiotic or antifungal or surgical intervention	life-threatening e.g., septic shock
IN4	Abscess	no		yes		
		(also code Infection if it applies)				
	LIVER					
LI0	Bilirubin	≤ ULN		< 1.5 x ULN	1.5 - 3.0 x ULN	> 3.0 x ULN
LI1	Transaminase (SGOT,SGPT)	≤ ULN	≤2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 20.0 x ULN	> 20.0 x ULN
LI2	Alk Phos or 5' nucleotidase	≤ ULN	≤ 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 20.0 x ULN	> 20.0 x ULN
LI3	Liver - Clinical	no change from baseline			precoma	hepatic coma
LI9	Liver - Other (specify)		mild	moderate	severe	life-threatening
	LUNG					
LU0	Dyspnea	no change		SOB on significant exertion	dyspnea at normal level of activity	dyspnea at rest
LU1	p02/pCO2	no change or p02 > 85 and pCO2 ≤ 40	p02 > 70 and pC02 ≤ 50, but not Grade 0	p02 > 60 and pCO2 ≤ 60, but not Grade 0-1	p02 > 50 and pCO2 ≤ 70, but not Grade 0 - 2	p02 ≤ 50 or pCO2 > 70
LU2	CO Diffusion Capacity	> 90% of pretreatment value	decrease to 76 - 90% of pretreatment	decrease to 51 - 75% of pretreatment	decrease to 26 - 50% of pretreatment	decrease to ≤ 25% of pretreatment
LU3	Pulmonary Fibrosis	normal	radiographic changes, no symptoms		changes with symptoms (also code symptoms)	
LU4	Pulmonary Edema	none			radiographic changes and diuretics required	requires intubation
LU5	Pneumonitis (non-infectious)/ Pulmonary Effusions/ Infiltrates	normal	radiographic changes, symptoms do not require steroids	steroids required or tap of effusion	oxygen required	requires assisted ventilation
LU6	Cough	no change	mild, relieved by OTC meds	requires narcotic antitussive	uncontrolled coughing spasms	
LU9	Lung -Other (specify)		mild	moderate	severe	life-threatening
	METABOLIC					
ME0	Hyponatremia	no change or > 135	131-135	126-130	121-125 (also code any CNS toxicities which apply)	≤ 120
ME1	Hypokalemia	no change or > 3.5	3.1-3.5	2.6-3.0	2.1-2.5 (also code Cardiac if applicable)	≤ 2.0
ME2	Hyperglycemia	< 116	116-160	161-250	251-500	> 500 or ketoacidosis
ME3	Hypoglycemia	> 64	55-64	40-54	30-39	< 30
ME4	Amylase	≤ ULN	< 1.5 x ULN	1.5-2.0 x ULN	2.1-5.0 x ULN	> 5.0 x ULN
ME5	Hypercalcemia	< 10.6	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
ME6	Hypocalcemia	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	≤ 6.0
ME7	Hypomagnesemia	> 1.4	1.4-1.2	1.1-0.9	0.8-0.6	≤ 0.5
ME8	Hypothyroidism	no	TSH elevated, asymptomatic, no therapy given	Symptomatic; thyroid hormone replacement therapy given	Patient hospitalized for manifestations of hypothyroidism	Myxedema coma
ME9	Metabolic- Other (Specify)		mild	moderate	severe	life-threatening

Codes	Toxicity	GRADE 0	1	2	3	4
	MUCOSAL					
MU0	Stomatitis	none	painless ulcers, erythema or mild soreness	painful erythema, edema, or ulcers, but can eat solids	painful erythema edema, or ulcers and cannot eat solids	requires parenteral or enteral support
MU1	Pharynx/ Esophagitis	none	painless ulcers, erythema, mild soreness or mild dysphagia	painful erythema, edema, or ulcers or moderate dysphagia but can eat solids	cannot eat solids	requires parenteral or enteral support or complete obstruction or perforation
MU2	Vaginitis	none	(same definition as Other Mucositis)			
MU3	Pseudomembranes	none			yes	
MU9	Other Mucositis (specify site)	none	erythema, or mild pain not requiring treatment	patchy & produces serosanguinous discharge or requires non-narcotic for pain	confluent fibrinous mucositis or requires narcotic for pain or ulceration	necrosis
	NEUROLOGIC/NEUROCENTRAL					
NC0	Disorientation	normal	confusion or disorientation, easily reoriented, some change in activity	confusion or disorientation requiring supervision	confusion or disorientation requiring institutionalization; or hallucinations	
NC1	Somnolence/ Agitation	normal	somnolence or agitation, non-disabling change in activity	somnolence or agitation, requires care-giver	somnolence or agitation, requires institutionalization	coma
NC2	Personality Change	no change	change, not disruptive to pt or family	disruptive to pt or family	harmful to others or self	psychosis
NC3	Convulsions	normal	focal seizure without impairment of consciousness	focal seizure with impairment of consciousness	generalized seizure, tonic-clonic or absence attack	seizure with loss of consciousness > 10 min
NC4	Malaise/ Fatigue/Lethargy	none	mild, able to continue normal activities	change in normal daily activity	in bed or chair > 50% of waking hrs	
NC5	Anxiety/ Depression	normal	mild, able to continue normal activities	change in normal activity	unable to function	suicidal
NC6	Cerebral Necrosis	none				present
NC8	Neurocortical - Other (specify)		mild	moderate	severe	life-threatening
NC9	CNS - Other (specify)		mild	moderate	severe	life-threatening
	NEUROMOTOR					
NM0	Weakness	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
NM1	Incoordination/ Ataxia	normal	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, nystagmus	locomotor ataxia	
NM2	Speech Impairment	normal		slurred speech	expressive aphasia or severe difficulty communicating	mute
NM3	Cerebellar Necrosis	no				present
NM8	Neurocerebellar - Other (specify)		mild	moderate	severe	life-threatening
NM9	Neuromotor Other (specify)		mild	moderate	severe	life-threatening

Codes	Toxicity	GRADE 0	1	2	3	4
	NEUROSENSORY					
NS0	Paresthesia	normal	mild paresthesia	moderate paresthesia, non-disabling	disabling paresthesia (interferes with function)	
NS1	Numbness/ Other PNS	normal		non-disabling objective sensory loss	disabling objective sensory loss	
NS2	Reflexes	normal	diminished reflexes	loss of deep tendon reflexes		
NS3	Hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correct-able
NS4	Vision	none or no change		nyctalopia with normal vision in normal light	symptomatic subtotal loss of vision or blurred vision in normal light	blindness
NS5	Taste	normal	slightly altered taste metallic taste	markedly altered taste		
NS9	Neurosensory - Other (specify)		mild	moderate	severe	life-threatening
	NEURO - OTHER					
NR0	Headache	none	mild	moderate, or severe but transient	unrelenting and severe	
NR1	Dizziness/Vertigo	none	non-disabling		disabling	
NR2	Insomnia	normal	occasional difficulty sleeping, may require sleeping pills		difficulty sleeping despite medication	
NR3	Restlessness	normal		requires sedation		
NR4	Arachnoiditis	no			yes (also code symptoms)	
NR9	Neuro - Other (specify)		mild	moderate	severe	life-threatening
	PAIN					
PA0	Other Pain (specify site)	normal	non-narcotics	oral narcotics	parenteral narcotics	uncontroll-able
PA1	Bone Pain		(Same definitions as Other Pain)			
PA2	Tumor Flare (also code Hypercalcemia if it applies)	none	pain requiring non-narcotic or redness or increase in tumor size		(Grade 2 - 5 same definitions as Other Pain)	
PA3	Abdominal Pain		(Same definitions as Other Pain)			
	RENAL/BLADDER					
BL0	Incontinence	normal	with coughing, sneezing, etc.	spontaneous, some control	no control	
BL1	Dysuria	none	mild pain	painful or burning urination, controlled by pyridium	not controlled by pyridium	
BL2	Urinary Retention	none	urinary residual > 100cc or occa-sionally requires catheter or diffi-culty initiating urinary stream	self catheterization always required for voiding	surgical procedure required (TUR or dilatation)	
BL3	Increased Frequency/ Urgency	no change	increase in frequ-ency or nocturia up to 2x normal	increase > 2x normal, but < hourly	with urgency and hourly or more, or requires catheter	
BL4	Hemorrhagic Cystitis	none	blood on microscopic exam	frank blood, no treatment required	bladder irrigation required	requires cystec-tomy or transfu-sion (also code hemorrhage)

Codes	Toxicity	GRADE 0	1	2	3	4
BL5	Bladder Cramps	none		yes (Code pain if applicable)		
BL9	Bladder - Other (specify)		mild	moderate	severe	life-threatening
RE0	Creatinine	≤ ULN	< 1.5 x ULN	1.5 - 3.0 x ULN	3.1 - 6.0 x ULN	> 6.0 x ULN
RE1	Proteinuria	no change	1+ or < 0.3 g% or < 3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or > 1.0 g% or > 10 g/l	nephrotic syndrome
RE2	Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion (also code hemorrhage)
RE3	Renal failure					dialysis required
RE9	Renal - Other (specify)		mild	moderate	severe	life-threatening
GU0	Ureteral Obstruction	none	unilateral, no surgery required	bilateral, no surgery required	not complete bilateral, but stints, nephrostomy tubes or surgery required	complete bilateral obstruc-tion
GU1	GU Fistula	none			yes	
GU9	GU - Other (specify)		mild	moderate	severe	life-threatening
	MISCELLANEOUS					
M00	Alopecia	no loss	mild hair loss	pronounced or total hair loss		
M01	Weight Gain	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	
M02	Weight Loss	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	
M03	Laryngitis	normal	mild or intermittent hoarseness	persistent hoarseness; able to vocalize	whispered speech	tracheostomy or intubation
M04	Salivary	normal	mild mouth dryness or slightly thickened saliva	moderate to complete dryness		acute salivary gland necrosis
M05	Anorexia	no	yes (also code Weight Loss if it applies)			
M09	Dehydration	no	dry mucous membranes, diminished skin turgor	requires IV fluid replace-ment (brief)	requires IV fluid replacement (sustained); hospitalization	hypotensive; requires in-tensive care; hemo-dynamic collapse
			(also code applicable cause, if known)			
M07	Wound Dehiscence	no	skin or subcutaneous		fascial	
M08	Wound necrosis	no			yes	
M06	Rectal laceration	no			yes	
M99	Miscellaneous-Other (specify)		mild	moderate	severe	life-threatening

Last Revised 12/94 ds/mb

APPENDIX 19.2

STAGING CRITERIA

TUMOR (T), NODE (N), METASTASES (M) CLASSIFICATION
PROSTATE CANCER

DEFINITIONS

Primary Tumor (T)

TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Clinically inapparent tumor not palpable or visible by imaging
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2		Palpable tumor confined within prostate*
	T2a	Tumor involves half of a lobe or less
	T2b	Tumor involves more than half of a lobe, but not both lobes
	T2c	Tumor involves both lobes
T3		Tumor extends through the prostatic capsule**
	T3a	Unilateral extracapsular extension
	T3b	Bilateral extracapsular extension
	T3c	Tumor invades seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles
	T4a	Tumor invades external sphincter and/or bladder neck and/or rectum
	T4b	Tumor invades levator muscles and/or is fixed to pelvic wall.

Lymph Node (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

Distant Metastasis (M)***

MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph nodes
	M1b	Bone
	M1c	Other sites

---

* Note: Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging is classified as T1c.

** Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

*** Note: When more than one site of metastasis is present, the most advanced category (M1c) is used.

APPENDIX 19.3

RISK FACTORS FOR CORONARY HEART DISEASE

1. Family history of premature CHD, cerebrovascular or occlusive peripheral vascular disease (definite onset before the age of 55 years in a sibling, parent, or sibling of a parent).

2. Cigarette smoking (currently smokes more than 10 cigarettes per day).

3. Hypertension

4. Low HDL-cholesterol concentration (below 35 mg/dl confirmed by repeat measurement).

5. Severe obesity (≥ 30% overweight).*

6. Diabetes mellitus.

7. History of definite cerebrovascular or occlusive peripheral vascular disease.

*Please use the Ideal Body Weight (IBW) as the baseline weight for calculating. The IBW should be calculated according to the following formula:

Estimation of IBW. Body weight and height are measured directly.

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

APPENDIX 19.4

PATHOLOGY REVIEW PROCEDURES

BACKGROUND

Since the primary endpoint of this study is the occurrence of histologically-proven prostatic carcinoma, the necessity for thorough and uniform histopathologic analysis of all diagnostic biopsies and surgical resection specimens assumes more importance than might be the case in other clinical trials. It is anticipated that this study will present unusual demands on diagnostic pathology techniques and interpretations that will, in turn, require extraordinary efforts to insure that satisfactory data are obtained. These demands are expected for the following reasons:

1. Participants placed on the study will have been carefully screened for the presence of prostatic carcinoma prior to entry. Tumors that develop during the course of the study will, therefore, likely be of very small volume. This will complicate biopsy interpretation since only small numbers of malignant cells may be present to confirm a diagnosis of cancer. Likewise, the examination of radical prostatectomy specimens will also require that the entire prostate will have to be inspected to determine tumor volumes or detect and quantitate capsular penetration.

2. The treatment of participants with finasteride will likely induce morphologic changes in benign and malignant prostate cells that complicate the diagnostic process. At present no published description of finasteride-induced changes is available to provide the community of institutional diagnostic pathologists with adequate diagnostic criteria.

3. The potential basic science study of the material derived from these participants is expected to be of great potential significance. For this reason it will be necessary to preserve as much as possible of the needle biopsy specimens (both benign and malignant) and the radical prostatectomy specimens. All of the residual tissue following routine histopathologic analysis will be archived for future study under the regulation of an appropriate experimental oversight committee.

To address these difficulties an unusually rigorous approach to the analysis of tissue specimens from participants on this protocol is felt to be justified. It is anticipated that some diagnostic pathology laboratories will be unable or unwilling to provide such detailed and time consuming services. An Anatomic Pathology Core Laboratory is therefore available to process specimens from all patients entered into the study according to the precise protocol described herein.

Protocol for Histopathologic Processing

Needle Biopsy Specimens:

Each needle biopsy core will be fixed for a minimum of four hours and a maximum of 48 hours in 10% neutral buffered formalin after which it will be processed for routine paraffin embedding. After paraffin infiltration, each core from the clinically prescribed sextant biopsies and any additional biopsies from otherwise suspicious areas will be embedded in an individual cassette. Care must be taken to align the tissue cores parallel to the paraffin block face to provide the maximum amount of tissue in each histologic section.

Following embedding each block will be sectioned to optimize the amount of tissue reserved for future study while being careful to avoid compromising diagnostic accuracy. Each paraffin block will be "faced" only to the point where the first complete sections are obtained. A "ribbon" of three sections will then be picked up on a 1" x 3" glass slide and designated as "Level 1". A second ribbon of three sections will be picked up on another slide and also designated as "Level 1". Each of the next eight sequential sections will be picked up on serially labeled "Plus" or poly-L-Lysine coated slides and reserved as unstained sections. The next two ribbons of three sections each will be picked up and designated as "Level 2". Again the next eight sequential sections will be picked up on serially labelled "Plus" slides and reserved. Finally, the next two ribbons of three sections will be picked up and designated as "Level 3". Levels 1, 2, and 3 (six slides total) will be stained with routine hematoxylin and eosin for conventional histopathologic interpretation. In the event that no additional sections are required from the paraffin block, the face will be sealed with a brush and molten paraffin.

If sections between the designated Levels are needed, they may be used as necessary for diagnosis. For example, immunohistochemical stains for basal cell specific cytokeratin may be required to determine whether or not suspicious or atypical acini contain basal cells and are, therefore, benign. After a diagnosis has been reached, one set of the H & E stained slides and all of the remaining unstained sections will be forwarded with the sealed paraffin blocks to the Pathology Core Laboratory for archival storage. If additional sections are required for diagnostic purposes at any time in the future, they may be requested directly from the Pathology Core Laboratory and will be shipped by overnight mail service whenever possible.

Radical Prostatectomy Specimens

Following surgery, the prostate should be weighed and measured (apex to base, anterior to posterior, left to right) in the fresh state as quickly as possible. The right side should then be painted with green Davidson ink (Bradley Products, Inc.) and the left side with blue Davidson ink. The entire specimen should then be coated with India ink and dipped into 5% acetic acid to fix the inks to the surface. The gland should then be suspended by string to fix in at least ten volumes of 10% neutral buffered formalin. Fixation should be allowed to proceed for a minimum of three days and a maximum of five days.

Following fixation, the gland should be sliced at 4 mm intervals from apex to base in the transverse plane (perpendicular to the posterior surface). Each slice is then identified by an ascending letter of the alphabet with the apical slice designated as "A". Following embedding, two histologic sections will be obtained from the proximal side of each slice and picked up on 3" x 2" glass slides. In the event that the histologic section of prostate is too large to fit on the oversized slides, the prostate slide should be divided into left and right halves through the urethra prior to embedding. These blocks should be labeled as X1 (left) and X2 (right), where X is the appropriate letter of the alphabet for that section. After sectioning the cut surface of the block face should be painted with molten paraffin to permit archival storage. After the Pathology Report is written, one set of the histologic slides and all the paraffin blocks will be sent to the Pathology Core Laboratory for archival storage.

TURP Specimens:

It is anticipated that some participants may undergo transurethral resection of their prostates for benign obstructive disease during the course of the study. Some of these patients may be found to have Stage A carcinoma in their resection specimens. In any case, all of the tissue resected should be submitted for histologic processing at the originating institution. If the institution is unwilling to process the entire specimen, the wet, fixed TURP fragments can also be submitted to the Pathology Core Laboratory.

The fresh prostate chips will be fixed in 10% neutral buffered formalin for a minimum of 24 hours and a maximum of 72 hours. Following fixation, the chips will be processed for routine paraffin embedding. All of the paraffin infiltrated chips will be embedded, using as many cassettes as required to sample every chip. Following embedding, each paraffin block will be faced until all the chips are exposed. Two histologic slides will be made from each block for diagnostic purposes, then the block faces will be sealed with molten paraffin. After diagnosis has been made, one set of the histologic slides and all the paraffin blocks will be sent to the Pathology Core Laboratory for archival storage.

Pathology Submission:

Pathologic specimens are to be sent to the Pathology Core Laboratory for central pathology review within 30 days of the diagnostic/therapeutic procedures. Shipment of the specimens can be charged to the Pathology Core Laboratory Federal Express account. Call the Pathology Core Laboratory for account information and/or a supply of pre-addressed Federal Express airbills.

Before specimens are shipped, notify the Pathology Core Laboratory of the intent to ship tissues by FAX transmission (FAX # 303/316-9084). The FAX will include the date and time of shipment and the airbill number. The airbill number will be confirmed with Federal Express at appropriate intervals following shipment to decrease any possibility of accidental loss.

Ship materials to:

Prostate Diagnostic Laboratory
4525 East 8th Avenue
Denver CO 80262
Phone: 303/316-9130 Main Laboratory
303/316-9158 Ginger Johnson

The pathology submission form, operative report and final institutional pathology report also need to be FAXed to the Statistical Center. See Section 7 of the Study Manual for instructions on the submission of the operative and pathology reports.

<u>"Wet" tissue</u>

If the originating institution cannot or will not prepare the tissue according to the protocol described above they may opt to submit all fixed tissue to the Pathology Core Laboratory for histologic processing. Prepackaged kits consisting of written instructions, appropriate specimen containers, and shipping materials will be provided to participating institutions from the Pathology Core Laboratory.

- Place specimens in appropriate vials
- Biopsies should be placed in small specimen vials, with one biopsy specimen per vial.
- Whole prostatectomy and TURP specimens should be placed in the large specimen vials.
- Label the vial with participant and site ID, participant initials (if possible), date, and biopsy location.
- Place the vials in the protective foam holder inside a white shipping box.
- Place the box inside a large resealable bag along with a "Dri-Mop" pad.
- Put the pad and box inside a FedEx Diagnostic Pack along with a copy of the Pathology Submission Form and the Operative Report.
- Seal and attach the FedEx shipping label
- Send the institutional pathology report to the Pathology Core Laboratory when it becomes available.

For pathology specimens which are processed by the Pathology Core Laboratory a complete set of H&E stained slides (prepared as described earlier in Appendix 19.4) will be returned to the originating institution for diagnostic purposes. <u>At the institution's request</u>, a *preliminary* evaluation of the specimen by a Pathologist at the Pathology Core Laboratory will be made available.

A pathologist at the Pathology Core Laboratory will be available for consultation regarding diagnostic questions related to these specimens. At any time following the receipt of stained sides by the originating institution, additional sections for diagnostic purposes may be requested from the Pathology Core Laboratory by FAX transmission. These requests will be met within one working day. All slides used for diagnostic purposes will remain with the originating institution, while one complete set remains with the Pathology Core Laboratory.

"Processed" materials

For those occasions when wet tissue can not be made available to the Pathology Core Laboratory, the following should be submitted for review and archival storage:

- One complete set of H&E stained sections
- All unstained paraffin sections
- All paraffin blocks
- Pathology submission form
- Operative report
- Pathology report

A Pathology Submission Checklist outlining the procedure can be found in Section 7 of the Study Manual.

APPENDIX 19.5

DRE, TRUS AND BIOPSY PROCEDURES

In the Prostate Cancer Prevention Trial (PCPT), digital rectal examination (DRE) is performed at the time of participant enrollment (First Visit) (DRE must be normal) and annually for a total of seven years. DRE is performed as one of two diagnostic tests to determine the presence of carcinoma of the prostate. If at any time during the study, DRE suggests the presence of prostate cancer, prostate biopsy is recommended.

Requirements of digital rectal examination are as follows:

1. The examination must be performed by a skilled and experienced examiner. The examiner need not be of a specific specialty but must be credentialed to perform the examination, must be well-trained in the performance of the examination and must have experience in the detection of subtle abnormalities of the prostate.

2. Participant position during digital rectal examination is based upon preference of the examiner. Acceptable positions include knee-chest, lateral, and leaning over an examination table. It is absolutely essential that the position allow complete examination of the entire surface of the prostate.

3. Digital rectal examination is performed by inserting the lubricated gloved finger (generally, index finger of dominant hand) into the rectum of the participant. (Various lubricants can be used but the one chosen should be non-irritating and non-allergenic.) The gland is then palpated over its entire rectal surface with attention directed for the presence of nodularity, induration, or asymmetry. The appropriate Study Form (see Study Manual) is then completed to illustrate the location of these areas in the prostate. The perimeter of abnormal areas are drawn and the area then characterized according to the legend on the form.

Transrectal ultrasound and prostate biopsy

Indications for transrectal ultrasound and biopsy (TRUS/biopsy) of the prostate during the PCPT:

1. Elevated Prostate Specific Antigen

2. Abnormal Digital Rectal Examination

3. Final biopsy at seven years.

At the time of TRUS/biopsy, the following procedures must be accomplished:

1. Prostate size measurement.

2. Evaluation for abnormal lesions.

   - hypoechoic peripheral lesions
   - other hypoechoic lesions
   - other observed lesions

3. Evaluation for extraprostatic prostate cancer.

The following guide is designed to describe characteristics of the location where TRUS/biopsy is performed, general characteristics of equipment, method of study, and method of prostate biopsy.

Characteristics of location

Transrectal ultrasonography and prostate biopsy (TRUS/biopsy) can be an apprehensive experience for any man. Similarly, it can be an embarrassing event. For these reasons, the location should emphasize participant privacy. Staff should provide professional support for the participant by explaining the procedure in advance and by querying the participant concerning his apprehensions during the procedure and by answering questions the participant may have.

Characteristics of equipment

A table is required for participant positioning during the procedure. Although the procedure usually requires only a few minutes, it is essential that the table be comfortable including the provision for a pillow for the participant's head. The participant is generally placed in a lateral decubitus position with the knees drawn up toward the chest.

Ultrasound equipment used for the examination can vary, depending upon the manufacturer. The probe used for the examination should be designed for transrectal examination of the prostate. Higher frequency probes (6.5 - 7 MHz range) will provide the best images of the prostate. An ideal probe is one which provides biplanar prostate examination and which provides a needle biopsy guide on the display screen. A method of maintaining "hard" copies of the examinations is required: these may include copies on thermal paper, on film, or on videotape. These copies must be filed in a manner such that they are labelled with the participant's identification.

Transrectal ultrasound probes are generally not sterilized prior to use. However, it is important that standard methods of cleaning and disinfecting the probe are employed. To minimize contamination of the probe, a condom is generally used over the tip. The hospital/clinic infection control policy should be consulted regarding the proper cleaning procedures.

Method of Study

Prior to TRUS, a digital rectal examination of the prostate is performed. This not only provides the ultrasonographer with a general impression of the prostatic anatomy, but also lubricates and dilates the anus prior to probe insertion. The participant should be asked to relax, not to bear down, and with gentle pressure, the probe is placed into the rectum. If a balloon is used, it is inflated at this time. The prostate is then scanned from apex to base including seminal vesicles in an axial plane. At its greatest diameter, a permanent copy is made. Additionally, if any intraprostatic lesions are noted, a permanent copy is made, the lesion marked, and measured.

The prostate is then examined in the longitudinal plane. Attention is directed toward the urethra, the trapezoidal region bounded by the bladder, seminal vesicle, and prostatic base, as well as for any intraprostatic lesions. A permanent copy is made of the prostate in the midline as well as of any intraprostatic lesions. Permanent copies are also made of any abnormalities of the seminal vesicles.

The following measurements should be made:

1. Maximum prostatic width - measured on axial examination.

2. Maximum prostatic antero-postero dimension - measured on longitudinal examination.

3. Maximum prostatic length - measured on longitudinal examination.

These measurements should be recorded on the appropriate Study Form.

Method of Prostate Biopsy

Prostate biopsy, performed using a transrectal approach, is performed to establish the presence of adenocarcinoma of the prostate. Biopsy should be performed under transrectal ultrasound guidance. Although larger needles which are manually operated can be employed, PCPT sites are encouraged to use automatic biopsy "guns" using 18G biopsy needles to obtain prostate core biopsies. Smaller needles are generally associated with less participant discomfort and possibly a reduced morbidity. Biopsy cores should be labelled according to their location and be placed in appropriate fixative immediately. (See Section 19.4.)

All participants must undergo at least six core biopsies of the prostate. Three scenarios for prostate biopsy are possible:

1. Abnormal digital rectal examination. If the participant has an abnormal DRE, a biopsy of the region of the abnormality is mandatory. The location of biopsy must be annotated on the appropriate Study Form. Following biopsy of area(s) of abnormal DRE, all additional zones of the prostate must be biopsied. If two areas of one zone have an abnormal DRE, two biopsies may be obtained from one zone. (Thus, at least six biopsies will be obtained in every participant.)

2. Abnormal transrectal ultrasound. All intraprostatic lesions demonstrable on ultrasound must undergo biopsy. The location of the lesion must be mapped on the appropriate Study Form. Prostatic zones which are normal on ultrasound similarly must undergo biopsy.

3. Normal DRE/Normal transrectal ultrasound. In these participants, standard "sextant" prostate biopsy is performed. Using ultrasound guidance, a single core is obtained from each zone of the prostate.

Appendix 19.6

PARTICIPATING STUDY CENTERS

The institutions listed here are the designated Study Centers for the PCPT. Each of these Study Centers may have affiliated Study Site(s) which will also be participating in the study. The Study Center, however, serves as the administrative and communications center. The Study Center is responsible for transmitting communications and administrative needs to its affiliated Study Site(s).

ALABAMA

University of Alabama at Birmingham
University of South Alabama Cancer Center MBCCOP

ARIZONA

Arizona Cancer Center
Greater Phoenix CCOP
Mayo Clinic Scottsdale CCOP

CALIFORNIA

Los Angeles Oncologic Institute
City of Hope National Medical Center
Desert Hospital Cancer Center
UC Davis Cancer Center/Bay Area CCOP/Santa Rosa CCOP
University of California, Irvine
University of California School of Medicine, San Francisco
Stanford University
Sutter Health Eastern
Kenneth Norris, Jr. Comprehensive Cancer Center at the University of Southern California

COLORADO

Colorado Cancer Research Program CCOP
University of Colorado Health Sciences Center

DELAWARE

Christiana Health Care Services (CCOP)

DISTRICT OF COLUMBIA

Walter Reed Army Medical Center

FLORIDA

University of Florida Shands Hospital Cancer Center
Mt. Sinai CCOP

GEORGIA

Atlanta Regional CCOP
Emory University/Grady Memorial Hospital CCOP

HAWAII

Hawaii MB-CCOP

ILLINOIS

Carle Cancer Center CCOP/Illinois ORA CCOP
Central Illinois CCOP
University of Chicago Cancer Research Center/Louis A. Weiss Memorial Hospital
Loyola University Medical Center
Research and Education Foundation of the Michael Reese Medical Staff
Northwestern Cancer Center Consortium/Evanston CCOP
Rush Medical Center

INDIANA

Methodist Cancer Program

IOWA

University of Iowa Hospitals and Clinics

KANSAS

Wichita CCOP

KENTUCKY

University of Kentucky Medical Center

LOUISIANA

Louisiana State University Medical Center - Shreveport
Louisiana State University Medical Center CCOP - New Orleans
Ochsner Cancer Institute CCOP

MASSACHUSETTS

Boston Medical Center
Dana Farber Cancer Institute
Tufts/New England Medical Center

MICHIGAN

Grand Rapids CCOP
Henry Ford Hospital - UCOP
Kalamazoo CCOP
University of Michigan Medical Center
Wayne State University

MINNESOTA

The Duluth CCOP
Mayo Clinic
Metro-Minnesota CCOP

MISSISSIPPI

University of Mississippi Medical Center

MISSOURI

Prostate Cancer Prevention Coalition (Kansas City CCOP)
Cancer Research for the Ozarks CCOP
St. Louis CCOP
St. Louis University

MONTANA

Montana CCOP

NEBRASKA

Creighton University Cancer Center CCOP/Cedar Rapids CCOP/Sioux CCOP

NEVADA

Southern Nevada CCOP

NEW HAMPSHIRE

Dartmouth-Hitchcock Medical Center

NEW JERSEY

Northern New Jersey CCOP
Cancer Center of Southern New Jersey Division of Medical Oncology
Cancer Institute of New Jersey - Hamilton

NEW MEXICO

University of New Mexico Cancer Center

NEW YORK

Brooklyn CGOP/The Methodist Hospital
County of Kings Minority Based PCPT Study Center (Kings County MBCCOP)
Long Island Jewish Medical Center/CALGB Consortium
North Shore University Hospital CCOP/CALGB Consortium
New York Hospital-Cornell Medical Center/CALGB Consortium
Roswell Park Cancer Institute/CALGB Consortium

NORTH CAROLINA

Southeast Cancer Control Consortium, Inc. (SE Cancer Consortium CCOP)
Wake Forest

NORTH DAKOTA

MeritCare Hospital CCOP

OHIO

Case Western Reserve University/Ireland Cancer Center
Christ Hospital Cancer Center
University of Cincinnati Medical Center
The Cleveland Clinic Foundation
Columbus CCOP
Dayton CCOP
Ohio State University
Toledo Area Prostate Cancer Prevention Trial (Toledo CCOP)

OKLAHOMA

Integris Troy and Dollie Smith Cancer Center
Saint Francis Hospital/Natalie Warren Bryant CCOP (Tulsa CCOP)

OREGON

Columbia River CCOP
Oregon Health Sciences University

PENNSYLVANIA

Fox Chase Cancer Center (CCOP)
Geisinger Clinical Oncology Program CCOP
Main Line Health CCOP
Mercy Hospital
University of Pennsylvania Cancer Center Hospital of the University of Pennsylvania
Prostate and Urologic Cancer Center (Pittsburgh Cancer Institute)
Temple University Cancer Center Consortium

RHODE ISLAND

The PCPT of Rhode Island

SOUTH CAROLINA

Greenville CCOP
Upstate Carolina CCOP

TENNESSEE

Baptist Hospital of East Tennessee
Vanderbilt University Medical Center

TEXAS

Brooke Army Medical Center (BAMC)
San Antonio Cancer Institute
Scott & White/Texas A&M CCOP
UT Southwestern Prostate Disease Center
Wilford Hall Medical Center (WHMC)

UTAH

University of Utah Medical Center

VERMONT

Green Mountain Oncology Group CCOP/CALGB Consortium
Vermont Cancer Center

VIRGINIA

Eastern Virginia UCOP/Sentara Cancer Institute at Sentara Norfolk General Hospital
Fairfax CGOP
Medical College of Virginia MBCCOP

WASHINGTON

Swedish Medical Center Tumor Institute
Virginia Mason CCOP/Northwest CCOP
University of Washington
Cancer Program - St. Joseph Hospital

WEST VIRGINIA

Camcare Health Education and Research Institute
West Virginia University at Morgantown/Mary Babb Randolph Cancer Center

WISCONSIN

Medical College of Wisconsin

Appendix 19.7

Diet Ancillary Study

A PROSPECTIVE COHORT STUDY OF DIET AND PROSTATE CANCER

1.0 OBJECTIVES

1.1 Primary Aim

To investigate whether dietary fat, assessed as intake of total fat, saturated fat and high fat foods, is associated with increased risk of prostate cancer.

1.2 Secondary Aims

a. To investigate whether fruits, vegetables and dietary fiber, assessed as servings of fruits, servings of vegetables and intake of dietary fiber is associated with decreased risk of prostate cancer.

b. To investigate the association of micro-nutrients, both from foods and nutritional supplements, with risk of prostate cancer.

c. To investigate the association of obesity, in particular upper body obesity, with risk of prostate cancer.

d. To examine whether the effect of finasteride on prostate cancer incidence is modified by dietary fat intake.

e. To validate a food frequency questionnaire when used in mature men.

To meet the Primary Aim and Secondary Aims a, b and c, we propose a prospective observational study based on dietary assessment at the year one visit only in the PCPT placebo group. To meet Secondary Aim d, we propose to examine the interaction of the diet and treatment with finasteride using the entire PCPT cohort (finasteride and placebo groups combined). To meet Secondary Aim e, we will compare multiple 24-hour diet recalls to food frequency results in a random sample of 150 PCPT participants.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Significance

Between 1973 and 1988 in the United States, there has been a 58 percent increase in the age-adjusted incidence of prostate cancer and an 8 percent increase in mortality. *(1)* In 1992, prostate cancer was the most common cancer in U.S. men, with 132,000 incident cases and 34,000 deaths. *(2)* Efforts to improve early detection through screening are ongoing, but many prostate tumors diagnosed through screening have already spread beyond the prostate. *(3)* Primary prevention of prostate cancer is thus a goal of enormous public health importance.

2.2 Dietary factors associated with prostate cancer

Fats, Saturated Fat or High-Fat Foods: International comparison studies of per capita food disappearance have found correlations between diet and prostate cancer mortality of 0.39 for meat and 0.69 for animal fat. *(4)* Analytic epidemiological studies of the relationship between diet and prostate cancer have been less consistent. At least 15 case-control studies and 7 cohort studies have been conducted on the relationship between foods or nutrients and prostate cancer. *(5 - 26)* Fat, saturated fat, or foods high

in saturated fat (meat or dairy products) were found to significantly increase prostate cancer risk in about two-thirds of the case-control studies and two cohort studies.

Fruits, Vegetables, Dietary Fiber and Associated Nutrients: Previous research has not separated intakes of fruits, vegetables and dietary fiber and we must therefore consider them together. International comparison studies of per capita food disappearance have found correlations between cereals and prostate cancer mortality of -0.75. *(4)* About one-third of the case-control studies have found a protective effect of high frequency of vegetable intake, ß-carotene intake, or vitamin C. *(5-8, 10-19, 27)* However other studies found a risk associated with high intakes of vitamin C or carotenes and one for fruit intake. *(13, 19, 20, 36)* Cohort studies provide more support with three of four studies reporting a protective effect of fiber-containing foods including green and yellow vegetables, rice, bread, beans/lentils/peas, fruits, nuts and tomatoes.

Mechanisms: Several mechanisms could explain a promotional effect of fat on prostate carcinogenesis, including effects on cell membrane composition, prostaglandin synthesis and hormone levels in blood or tissue. *(29)* Experimental studies suggest that low fat diets can alter the hormonal milieu in adult males. Fiber may act on hormone levels via its effect on the enterohepatic circulation of steroids. Dietary fiber may entrap steroids in the intestinal tract and prevent their reabsorption. *(30)*

3.0 METHODS

3.1 Overview

This prospective cohort study of the relationships of diet, nutritional supplement use and obesity with the risk of prostate cancer. We are adding three sets of measures to the PCPT at the one-year post-randomization visit only: 1) usual dietary intake of macro- and micronutrients; 2) nutritional supplement use; and 3) adiposity, including distribution of adiposity. Principal study results will be based on analyses of 9,000 control group participants (specifically the 5,400 control group men who are expected to receive prostate biopsies at the end of the study. We will estimate the relative risk of histologically-proven prostate cancer using logistic regression models in which disease outcome at seven years is the dependent variable; the independent variable set consists of variables indicating level (categorized) of nutrient intake and covariates include confounding factors (e.g., total energy intake, age, race and family history of prostate cancer). Additional analyses will incorporate data from the intervention group to assess: 1) the relationship of diet with prostate cancer in persons treated with finasteride; and 2) the effect modification by diet of the relationship between finasteride and prostate cancer. We will validate dietary and nutritional supplement assessment instruments in a substudy of participants who will complete six, 24-hour dietary recalls over a one year period. Measures, questionnaires, quality control, validity studies and statistical analyses are described below.

Figure 1 shows a schedule of key measures for the PCPT (shown as O's) and for the diet study described here (shown as X's). Below we describe those measures related to the diet ancillary study.

3.2 Diet Measurement

Selection of dietary assessment instruments: Assessment of nutrient intake in free-living populations is a difficult problem in epidemiologic research. There are no "gold standard" or criterion measures, and each of the standard methods (food diaries, dietary recalls, food frequency questionnaires) differs in reliability, accuracy, costs, participant burden and susceptibility to bias. In this study, we propose to use self-administered food frequency questionnaires for the following four reasons. First there is good evidence that FFQs can give reasonably valid estimates of the macronutrients (percent of energy from

fat, saturated fat, polyunsaturated fat), micronutrients (beta-carotene and vitamin C) and other dietary factors (fiber, usual servings of fruits and vegetables) of interest in this study. *(31)* Second, FFQs are the only dietary intake measure that minimizes the very high intra-individual, day to day variability in nutrient intake without using the average of multiple assessment (e.g., a 7-day food diary). Third, FEQs are the only practical approach to dietary assessment in very large, prospective studies. *(32)* For example, we estimate that adding two, four-day food records to this study would cost an additional 17.9 million dollars in direct costs. Fourth, FFQs have relatively low participant burden. Careful completion takes approximately 25 minutes and the quality control review takes only one to two minutes.

Description of Food Frequency Instrument

For this study, we propose to use a modification of the FFQ developed for the Women's Health Initiative. In format, this FFQ is based on the National Cancer Institute/Block FFQ, further revised for processing with the DataFax system. *(33)* The nutrient database used to convert food frequency information into nutrients is from the University of Minnesota's Nutrition Coding Center database, and the computer algorithms for analysis were developed at the Fred Hutchinson Cancer Research Center. *(34)* We have recently completed modifications of this FFQ for use in African-American, Latino and lower socioeconomic status populations in the "Women's Health Trial: Feasibility Study in Minority Populations" (WHT:FSMP).

Nutrient Analysis of FFQs

The nutrient database used by the FHCRC FFQ software is derived from the University of Minnesota Nutrition Coding Center nutrient database. The primary source for nutrient values in this database are the USDA Nutrient Database for Standard Reference (1987) and its periodic revisions. Our approach to generating an FFQ database is described elsewhere. *(32)* Table I gives the relevant variables that are calculated from this analysis system.

3.3 Nutritional Supplement Use

We will assess use of dietary supplements as part of the FFQ booklet. We will use a self-administered form to capture type, frequency and duration of supplements presently used. We will also collect data on use of other supplements during the previous five years, in order to better separate regular, long-term supplement users from others.

3.4 Anthropometry

The PCPT trial protocol includes assessments of height and weight at baseline, and weight at each subsequent annual visit. We will collect, at one year, four measures of body girth as measures of upper body obesity: abdomen, waist, hip and thigh circumferences. The motivation for measuring adiposity and the proposed measures of upper body obesity are described below.

Measures of adiposity: For epidemiologic studies, weight controlled for height and body mass index (the ratio of weight to height squared) are good, general indices of body adiposity and correlate well with more direct measures of total body fat mass such as underwater weighing. *(29)* In epidemiologic studies these measures predict many morbidity endpoints. *(35)* The pattern of distribution of adiposity has important metabolic consequences and distribution of fat predominantly in the abdominal region (so-called upper body obesity) may be more important in this study than total adipose mass. There is some controversy in the literature on the best measure of upper body obesity. While for women the ratio of waist to hip circumference appears to correlate well with biologic measures such as serum cholesterol, for men the ratio of waist to thigh may be superior. *(36)* In addition, for men measures at the waist (iliac crest) may underestimate upper body

fat. Because these measures are simple and non-invasive, we propose to measure both abdomen and waist and both hip and thigh circumferences.

Figure 1. Exposure and Covariant Assessments, Through Month 48 of PCPT

	Enroll-ment	Random-ization									Contin-uation to be propo-sed
	-3	0	3	6	9	12	15	18	21	24	48
ALL PARTICIPANTS											
Demographics											
Age, race, education	0										
Risk Factors											
Family and medical history, smoking, vasectomy, alcohol, physical and sexual activity	0										
Antropometry											
Height, weight	0					0					0
Waist, hip and thigh circumferences						X					
Serum											
PSA	0					0				0	0
Cholesterol	0										
Serum Bank	0					0				0	0
Nutrients											
Food frequency questionnaire						X					X
Nutritional supplement questionnaire						X					X
VALIDITY STUDY (SUBSAMPLE)											
Nutrients											
24-hour recalls							X	X	X	X	X X
Food frequency questionnaire										X	
Nutritional supplement questionnaire										X	

X = Additions for Diet Study

0 = Part of PCPT protocol

3.5 Covariates

All covariates of interest for this study are collected as part of the PCPT protocol. These variables include: age, race, smoking and alcohol use; physical activity; education, family history of prostate cancer; participant history of chronic disease (cancer, cardiovascular disease, diabetes, hypertension), history and date of vasectomy; and PSA.

3.6 Validity Substudy

The purpose of validity research is to establish the measurement characteristics of the FFQ when used in the PCPT participant sample. We have sample data on the reliability and validity of similar FFQs when used in samples of women, but data on validity and reliability are more limited in men. Also, the PCPT will emphasize recruitment from a broad range of socioeconomic and racial groups, and it will be important to evaluate the FFQ's measurement characteristics more extensively in these populations. Finally, there is an agreement among nutritional epidemiologists that it is important to incorporate a substudy to evaluate the measurement characteristics of any dietary assessment tool when it is the sole measure of diet in a large epidemiologic study. *(37)* Such substudies can provide important support for the interpretation of study results.

Selection of Dietary Assessment Instrument: We will validate the PCPT FFQ against six, 24-hour dietary recalls. We selected dietary recalls instead of multiple-day food diaries for several reasons. First, 24-hour recalls can be administered over the telephone, so that collection and analysis in this multicenter trial can be centralized and standardized without having professional nutritionists at each clinical site. Second, nutrient intake assessment with the only alternative criterion measure, multiple-day diet records, requires extensive participant training and cooperation and carries a very high participant burden. Third and most importantly, 24-hour dietary recalls can be unannounced (not scheduled in advance), so that the bias towards temporary changes in diet due to record-keeping can be minimized. While participants could misreport their dietary behavior during a recall, they cannot change their behavior from the previous day. Finally, we believe that we can recruit a less biased sample of participants into the validity substudy using dietary recalls, because they need only respond to questions during 20 minute phone interviews and need not come to the clinic for training and then return for record reviews.

We plan a substudy in a random sample of 150 PCPT participants. We will administer six 24-hour recalls to each substudy participant, spread evenly between years one and two of the PCPT. Two of these recalls will be on Monday, to include weekend days and all recalls will be unscheduled. If a participant cannot complete a recall when contacted, we will make additional, unscheduled attempts. We expect to complete at least five recalls on 75 percent of the sample, which will yield 115 persons for analysis. At the end of the substudy protocol, we will compensate substudy participants $100 for their time. Validity substudy participants will also complete an additional FFQ before the 24-month visit. This FFQ will cover the time period over the previous year, and serve as one of the comparison measures for the multiple, 24-hour dietary recalls. We will also use this FFQ to estimate the test-retest reliability, assuming that participants' diets should not change substantially over the one year time period.

3.7 Endpoint

The endpoint for this study will be histologically -proven presence or absence of prostate cancer, assessed for most participants at the termination of the trial. The majority of prostate cancer cases detected will be asymptomatic.

3.8 Final sample and sample size

The control group is the primary group of interest for the proposed study of diet and prostate cancer. The intervention group is of less interest for several reasons: 1) finasteride may affect diet or weight, e.g., some hormone treatments lead to weight changes; and 2) if lower dietary fat intake and finasteride both reduce the risk of prostate cancer through hormonal mechanisms, there may be an interaction between the effect of diet and finasteride on prostate cancer. Although our primary analysis will be among control men, we will collect all measures on intervention and control groups given the blinded nature of the PCPT design. We do plan to analyze separately the results in the intervention group.

Only men with a positive biopsy before the end of the trial or a biopsy (positive or negative) at seven years will be considered to have endpoint information. The PCPT estimates that 5,400 (60%) of the 9,000 control men will have complete exposure and endpoint information. This is based on the following: 20% mortality (seven-year mortality of U.S. men age 55 - 70, median age 63); 15% loss to follow-up (our experience in the CARET trial); and 5% biopsy refusal at seven years.

3.9 Data analysis and study power:

As an example of our analytic approach, we present the analysis for the first part of the primary specific aim: the investigation of the association of total dietary fat intake with prostate cancer.

Choice of Statistical Model. We will analyze the association between dietary fat intake and histologically proven presence or absence of prostate cancer using the logistic regression model:

$$ln\left(\frac{pr(d)}{1-pr(d)}\right) = \alpha + \beta 1\, x1 + \beta 2\, x\, 2 + \beta 3\, x\, 3 + ...$$

The logistic model allows estimation of the effect of the factor of interest (x_1), in this case fat intake, on probability of disease (pr(d)), while controlling the effects of other factors (x_2,x_2....).

We plan to control for age, race, family history and other confounding factors identified during analysis. Parameters in the model will be estimated using maximum likelihood techniques. *(38)*

We plan two approaches to parametizing fat intake. First, we will express fat intake as total energy from fat and we will adjust for total energy from other macronutrients (carbohydrate, protein and alcohol). Second, we will express fat intake as percent of energy from fat. We will model the association between fat intake and prostate cancer by categorizing the fat measure into quartiles (using indicator variables in the model), and we will calculate the odds ratios of prostate cancer and their 95% confidence intervals for each quartile of fat intake. We will also conduct a test for trend by representing percent energy from fat as a single variable coded 1 for quartile 1, coded 2 for quartile 2, etc., in the logistic model. This yields an overall estimate of the trend odds ratio for a one quartile increment in fat intake and yields a single significance test for the association of fat intake with prostate cancer. This is the logistic analog to the Mantel-Haenszel test for trend.

We will use similar models to analyze the other variables in the primary specific aim, saturated fat intake and servings of high fat meats and servings of high fat dairy foods, as well as secondary analyses a and b.

Association of Obesity, in Particular Upper Body Obesity with Risk of Prostate Cancer. We will analyze the association of obesity with prostate cancer using body mass index (BMI) (weight/height^2) in a logistic model with age, race and height as covariates. We include height as an adjustment factor to account for any remaining confounding of height with body mass index. We will evaluate four models of the association of upper body obesity with prostate cancer, using waist/hip, waist/thigh, abdomen/hip and abdomen/thigh ratios as the primary independent variables, controlling for age, race and body mass index. Including BMI in the model allows separation of any independent effect of upper body obesity from obesity per se. The analysis strategy will be similar to that described for the other exposures of interest; specifically, we will estimate individual odds ratios and confidence intervals for each quartile of obesity or upper body obesity and we will complete an overall test for trend.

Modification of the Effect of Finasteride by Dietary Fat. The final analyses for this study will be conducted to answer whether the effect of finasteride is modified by dietary fat intake. First, we will compute the odds ratios and 95% confidence intervals for the effect of finasteride on prostate cancer separately for the four groups of men categorized by quartiles of percent energy from fat. If these appear to differ (e.g., if finasteride is beneficial for men with the highest level of fat intake but not for those in the lowest level of intake), this is suggestive of modification of the finasteride effect by dietary fat intake.

Second, we will model the interaction between finasteride and dietary fat. To examine this interaction, we will model the relationship between dietary fat, treatment and prostate cancer in a logistic model using the entire study cohort. The model will include the main effect of treatment (finasteride vs. control) and the main effects of dietary fat and an interaction between the two, as well as covariates (age, race, energy intake). If consistent with the data, dietary fat will be modeled as a single trend variable (described under Primary Aim above). This simplifies the interaction, so that a single term would indicate whether the slope of any dietary fat effect on prostate cancer is different for the treatment versus the control group. We will use the interaction term coefficient (ß) and its standard error to determine the magnitude and significance of the modification of the finasteride effect by dietary fat.

Study Power and Minimal Detectable Odds Ratio. Because the sample size of this study is fixed by the PCPT, we present power calculations in terms of the minimal detectable difference in the rate of histologically proven prostate cancer between those in the upper quarter of fat intake (or any nutrient or food group intake), p_1, and the rate in lower quarter, p_0.

The difference was computed based on the standard power calculation formula for the difference between groups:

$$\Delta = \left| p_1 - p_0 \right| = \left(\frac{(Z_{0/2} + Z_{ß})^2 \cdot 2p\,(1 - p)}{n} \right)^{1/2}$$

This formula yields the minimal detectable difference in outcome, Δ, for a study with n subjects in the upper quartile of food intake and n subjects in the lower quartile. This difference can then be converted into a minimal detectable odds ratio, which can be interpreted as the minimal odds ratio for the upper quartile of intake versus lower quartile that will yield a 95% CI around the odds ratio that would exclude one.

The assumptions used in the computation were:

1. A two-sided significance level α equal to 5%.
2. Power (1-ß) equal to 80%.
3. The average outcome, p, in the combined upper and lower quartile of intake was assumed to be 6%. This is based on the PCPT estimate that 6% of the control group who have biopsies will have detectable prostate cancer at seven years.
4. The number of men in each quartile of intake, n, was assumed to be 1,350. This was based on 9,000 men to be randomized into the PCPT control arm (proposal), with 60% (5,400) having complete data.

Applying the above assumptions to the equation above yields d = .026. Translating this difference into p_0 and p_1 and an odds ratio (such that $(p_0 + p_1)/2 = .06$ and $p_1 - p_0 = .026$) yields $p_0 = .047$, $p_1 = .073$ and an odds ratio = 1.60. This suggests that the study will have 80% power to detect an odds ratio of prostate cancer of 1.6 for those in the upper versus lower quartile of fat intake or saturated fat intake.

Validity Substudy: Data Analyses and Power

Data Analyses. We will perform data analyses for the validity substudy on the combined sample of intervention and control men. We assume that, despite our concerns about inclusion of the intervention group in the main study, the drug will not affect accuracy of diet recall.

The data analyses and power calculations described below emphasize the estimation of the reliability and validity correlation coefficients and their lower bounds. This is because the goal of the validity study is to estimate with reasonable confidence the magnitude of the validity and reliability coefficients rather than simply whether the correlation coefficients differ from zero.

The analyses will be based on standard techniques for analysis of validity and reliability studies. *(39, 40)* Specifically, we will assess the reliability of the food frequency questionnaire by comparing the measures from the one-year post-randomization administration of the FFQ to the measures from the two-year administration of the FFQ, using the intraclass correlation coefficient. We will calculate intraclass correlation coefficients and their lower confidence bounds for each of the dietary measures listed in Table 1. In addition, we will divide participants into quartiles of intake based on the first and second FFQs and compare these using weighted kappa.

We will assess the validity (bias and precision) of FFQ measures by comparing the dietary measure from the average of the year 1 and year 2 FFQs (X_1) to the measure from the combined six (or at a minimum five) 24-hour dietary recalls completed between year one and year two (X_2). We will assess systematic bias in the FFQ (versus the recalls) as the difference between the mean FFQ measure in the substudy subjects and the mean measure from the six, 24-hour dietary recalls: $X_1 - X_2$. We will compute a confidence interval around this mean difference based on a one sample t-test on the variable $X_{i1} - X_{i2}$) computed for each subject i. We will assess precision as the Pearson correlation coefficient between X_1 and X_2, and its lower 95% confidence bound. We will estimate

bias and Pearson correlation coefficients for each dietary measure in Table 1. Those nutrients that are positively skewed will be ln transformed for the computation of the Pearson correlation. We will also compute weighted kappas after categorizing subjects into quartiles based on X_1 and quartiles of X_2.

3.10 Timeline

Data collection for the one-year visit begins in January 1995 and continues through December 1997. We will complete nutrient analyses of FFQs, clean the data and prepare analysis files between January and March of 1998. We will prepare the analysis plan and data documentation between April and May of 1998. The validity substudy will begin in Spring of 1995 and recruit participants evenly over one year. Validity substudy data collection will end in Spring of 1997, leaving adequate time for data analysis and manuscript preparation by the end of 1997.

4.0 LITERATURE CITED

1. Ries LAG, Hankey BF, Miller BA, Hartman AM, Edwards BK. Cancer Statistics Review 1973 - 1988. National Cancer Institute. NIH Publication No. 91-2789, 1991.

2. Boring CC, Squires TS, Tong T. Cancer Statistics, 1992. CA Cancer J Clin 42:19-38, 1992.

3. Catalona WJ, Smith D, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, Petros JA, Andriole GL. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. NEJM 324:1156-1161, 1991.

4. Rose DP, Boyar AP, Wynder EL. International comparisons for mortality rates for cancer of the breast, ovary, prostate and colon, and per capita food consumption. Cancer 58:2363-2371, 1986.

5. Graham S, Haughey B, Marshall J, Priore R, Byers T, Rzepka T, Mettlin C, Pontes JE. Diet in epidemiology of carcinoma of the prostate gland. JNCI 70:687-692, 1983.

6. Heshmat MY, Kaul L, Kovi J, Jackson MA, Jackson AG, Jones GW, Epson M, Enterline JP, Worrell RG, Perry SL. Nutrition and prostate cancer: a case control study. Prostate 6:7-17, 1985.

7. Mishina T, Watanabe H, Araki II, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. Prostate 6:423-436, 1985.

8. Talamini R, La Vecchia C, Decarli A, Negri E, Franceschi S. Nutrition, social factors and prostatic cancer in Northern Italian population. Br J Cancer 58:817-821, 1986.

9. Kaul L, Heshmat MY, Kovi J, Jackson MA, Jackson AG, Jones GW, Edson M, Enterline JP, Worrell RG, Perry SL. The role of diet in prostate cancer. Nutr Cancer 9:123-128, 1987.

10. Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE. Case-control studies of prostatic cancer in blacks and whites in Southern California. JNCI 78:869-874, 1987.

11. Ohno Y, Yoshida O, Ioshi K, Okada K, Yamabe H, Schroeder FH. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res 48:1331-1336, 1988.

12. Kolonel LN, Yoshizawa CN, Hankin JH. Diet and prostatic cancer: a case-control study in Hawaii. Am J Epidemiol 127:999-1012, 1988.

13. Mettlin C, Selenskas S, Natarajan N, Huben R. Beta-carotene and animal fats and their relationship to prostate cancer risk: a case-control study. Cancer 64:605-612, 1989.

14. Fincham SM, Hill GB, Hanson JH, Wijayasinghe C. Epidemiology of prostatic cancer: a case-control study. Prostate 17:189-206, 1990.

15. West DW, Slattery ML, Robison LM, French TK, Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. Cancer Causes Control 2:85-94, 1991.

16. Bravo MP, Castellanos E, del Rey Calero J. Dietary factors and prostatic cancer. Urol Int 46:163-166, 1991.

17. La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Boyle P. Dairy products and the risk of prostatic cancer. Oncology 48:406-410, 1991.

18. Walker ARP, Walker BF, Tsotetsi NG, Sebitso C, Siwedi D, Walker AJ. Case-control study of prostate cancer in black patients in Soweto, South Africa. Br J Cancer 65:438-441, 1992.

19. Talamini R, Franceschi S, La Vecchia C, Serraino D, Barra S, Negri E. Diet and prostatic cancer: a case-control study in Northern Italy. Nutr Cancer 18:277-286, 1992.

20. Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. Natl Cancer Inst Monogr 53:149-155, 1979.

21. Snowdon DA, Phillips RL, Choi W. Diet, obesity and risk of fatal prostate cancer. AM J Epidemiol 120:244-250, 1984.

22. Severson RK, Nomura AMY, Grove JS, Stemmermann. A prospective study of demographics, diet and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res 49:1857-1860, 1989.

23. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle and prostate cancer in Adventist men. Cancer 64:598-604, 1989.

24. Thompson MM, Garland C, Barrett-Connor E, Khaw K, Friedlander NJ, Wingard DL. Heart disease risk factors, diabetes and prostatic cancer in an adult community. Am J Epidemiol 129:511-517, 1989.

25. Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HTC, Blot WJ. Diet, tobacco use and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer Res 50:6836-6840, 1990.

26. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. A prospective study of dietary fat and risk of prostate cancer. JNCI 85:1571-1579, 1993.

27. Le Merchand L, Handkin JH, Kolonel LN, Wilkens LR. Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary beta-carotene. Am J Epidemiol 133:215-219, 1991.

28. Kolonel LN, Hankin JH, Yoshizawa CN. Vitamin A and prostate cancer in elderly men: enhancement of risk. Cancer Res 47:2982-2985, 1987.

29. National Research Council, Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences. Diet and Health: Implications for Reducing Chronic Disease Risk. Washington, DC: National Academy of Sciences, 1989.

30. Howie BJ, Shultz TD. Dietary and hormonal interrelationship among vegetarian Seventh-Day Aventists and nonvegetarian men. Am J Clin Nutr 42:127-134, 1985.

31. Willet W. Nutritional Epidemiology. New York: Oxford University Press. 1990.

32. Kristal AK, Shattuck AL, Williams AE. Food frequency questionnaires for diet intervention research. Proceedings of the 17th National Nutrient Databank Conference, Baltimore, MD, June 7 - 10, 1992. Washington DC, International Life Sciences Institute, 110-125, 1994.

33. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 43:1327-1335, 1990.

34. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc 88:1268-1271, 1988.

35. Bjorntorp P. The association between obesity, adipose tissue distribution and disease. Acta Med Scand 723 (Suppl):121-134, 1987.

36. Mueller WH, Wear ML, Hanis CL, Emerson JB, Barton SA, Hewett-Emmett D, Schull WJ. Which measure of body fat distribution is best for epidemiologic research? Am J Epidemiol 133:858-869, 191.

37. Report of Group A of the American Cancer Society Workshop on Cancer and Nutrition: Panel on Human Studies. Cancer Research 53:2449s-2451s, 1993.

38. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology. New York: Oxford University Press, 1986.

39. Armstrong BK, White E, Saracci R. Principles of exposure measurement in epidemiology, New York: Oxford University Press. 1992.

40. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley and Sons. pp. 1-32, 1986.

Appendix 19.8

CAG Repeat Length Ancillary Study

A PROSPECTIVE COHORT STUDY OF CAG REPEAT LENGTH AND PROSTATE CANCER

1.0 OBJECTIVES

1.1 Primary Aim

a. To assess the degree to which CAG trinucleotide repeat length is associated with an increased risk of prostate cancer. A shorter length is hypothesized to be associated with higher risk.

1.2 Secondary Aims

a. To investigate statistical models of prostate cancer risk as a function of CAG repeat length, ethnicity, race, family history, PSA level, age, arm, whether prostate cancer was discovered as a result of symptoms, and other potential explanatory factors.

b. To obtain confirmatory data on the association of CAG repeat length and racial and ethnic groups.

c. To obtain confirmatory data on the association (or lack there of) of CAG repeat length and family history of prostate cancer.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Epidemiology

Metastatic prostate adenocarcinoma is now the leading cause of malignancy in males in the United States and the second leading cause of cancer related deaths in that population (44,000 estimated deaths in 1997). It has been estimated that 15.4% of men will be diagnosed with prostate cancer at some point in their life, with 317,000 men diagnosed in the United States in 1997. *(1)* Moreover, the number of new cases of prostate cancer has shown a steady rise over the past 20 years. Because the population continues to age and effective prevention strategies have not emerged, prostate cancer will continue to represent a major public health issue in the decades ahead.

African-American males have a significantly higher risk for developing prostate cancer than non-African-American males. *(2 - 4)* When compared to other ethnic groups (i.e., Hispanics, caucasians, and Asians), African-American men have a lower five-year survival rate (49%) compared to U.S. caucasians (60%). In addition, they are more likely to have an initial diagnosis of metastatic disease (29.3% versus 17.8%), and present at an earlier age (70.3 years versus 72.3 years). *(5)* Several studies have shown that at the time of diagnosis, African-American patients have significantly higher clinical stages and tumor grades than U.S. caucasians. *(4, 6, 7)* While the reasons for these findings are unclear, socioeconomic factors, health care access and biological differences based upon ethnicity have all been identified. *(8, 9)*

2.2 Overview

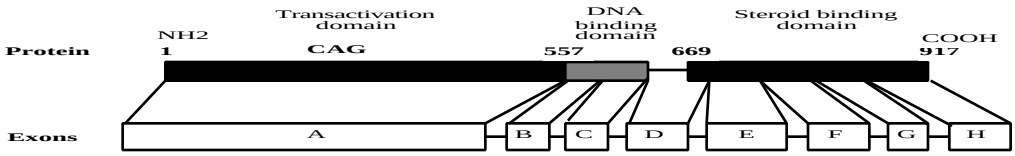
This prospective study will look for associations between the CAG trinucleotide repeat length in the androgen receptor and the relative risk of developing prostate cancer. In addition, it will study the relationship between CAG repeat length and racial/ethnic groups, aggressiveness of disease, positive family history for prostate cancer and age of onset. Individuals enrolled on the PCPT provide an ideal population for such a prospective study. All participants in this study are initially determined to be disease free by standard PSA screening and digital rectal exam. The trial is of sufficient duration, and the participants old enough, so that the incidence of detecting prostate cancer should be significant. This will allow us to determine if a relationship exists between CAG repeat length and the risk of prostate cancer development. Additionally, due to the diversity of the patient population, the relationship between trinucleotide CAG repeat length and any racial or ethnic associated risk can be assessed.

No additional measures are being added to the PCPT. Frozen serum has been previously stored on all participants enrolled on the study. Using frozen serum, genomic DNA will be isolated and the CAG repeat region of the androgen receptor will be amplified using polymerase chain reaction (PCR). The CAG repeat length will be calculated based on comparison to known standards and confirmed on a percentage of samples by direct DNA sequencing of the amplified fragments.

2.3 Molecular Studies Influencing Current Clinical Approaches

The androgen receptor gene is located on the X chromosome (q11 - 12) and is composed of eight exons encoding three separate functional domains (Figure 1): the amino terminal transactivation domain, the DNA binding domain, and the steroid binding domain. The androgen receptor is activated by binding of either testosterone or DHT to the steroid binding domain in the cytoplasm followed by a loss of bound heat shock proteins. The activated receptor translocates to the nucleus where it recognizes and binds to 16 base pair imperfect palindromic sequences, called androgen responsive elements (ARE), found within the promoter region of a target gene. Binding to an ARE is mediated by two “zinc fingers” located in the DNA binding domain. The formation of either a homodimeric androgen receptor or a heterodimer with other nuclear hormone receptors may be required for transactivation activity either prior to or following DNA binding. Dimerization as well as interaction with accessory proteins may provide a level of specificity or selectivity in the target genes activated in a particular cell type. The transactivation domain interacts with the transcriptional machinery, and possibly other undetermined regions in the DNA, leading to changes in the transcriptional activity of a target gene. *(10, 11)* The androgen receptor is a 110 kDa protein belonging to a superfamily of ligand-responsive transcription regulators. Other members of this family include receptors for retinoic acid, triiodothyronine, vitamin D, and glucocorticoids. *(12)* Following activation by an agonistic ligand, androgen receptor stability is distinctly improved and serine/threonine phosphorylation occurs. *(13)* The physiological impact of these phosphorylated residues (serine 81, 94, and 650) is not clear, although some in vitro models have shown altered ligand binding transcriptional regulation upon phosphorylation. *(14)*

Fig. 1



2.4 CAG Repeat Region Background

The importance of hormones in regulating prostate cancer growth was established with the pioneering work of Huggins and Hodges in the 1940s. *(16)* Since that time, the critical role of the androgen receptor in mediating androgen hormone action has been increasingly recognized. In recent years, mechanistic studies of androgen receptor actions have shown that this protein functions as a ligand-dependent transcriptional regulator. *(17)* A number of studies demonstrate the importance of transcriptional regulation in the control of prostate growth and apoptosis. *(18)*

The androgen receptor, like all steroid hormone receptors, contains three functional domains. *(17, 19)* These domains include a steroid binding domain, a DNA binding domain, and a transactivation domain. Following the cloning of the androgen receptor cDNA, it was observed that the transactivation domain contains a number of CAG trinucleotide repeats encoding a homopolymeric stretch of glutamine residues. *(19)* This homopolymer region is polymorphic in the population varying between 11 and 31 CAG repeats. *(20)*

Individuals with an expanded CAG repeat length (*40* - 62 repeats) in the androgen receptor are afflicted with Kennedy's disease, a rare form of X-linked spinobulbar muscle atrophy. *(21)* Subsequent studies have demonstrated that men with Kennedy's disease have mild androgen insensitivity. *(22)* The length of the CAG repeat region is inversely related to the transcriptional activity of target genes. Mhatre et al. demonstrated that androgen receptors with 40 to 50 trinucleotide repeats exhibit decreased transcriptional activation from AREs in vitro. *(23)* In addition, Chamberlain et al. demonstrated that an increase in trinucleotide repeats decreased transactivation function in vitro. *(24)* It is speculated that a longer repeat length allows the formation of nucleosomes in this region leading to a decrease in transactivation. Deletion of the endogenous 25 CAG repeats in the human androgen receptor resulted in higher transactivation activity in vitro. Therefore, it has been hypothesized that a decreased CAG length would have an increased ability to activate target genes in the genome resulting in altered growth regulation and the development of prostate cancer. *(25)*

2.5 CAG Repeat Length and Prostate Cancer Risk

Differences in androgen receptor CAG repeat length have been linked recently to prostate cancer risk. *(26 - 28)* In a study of men participating in the Physicians Health Study, a comparison was made between 368 men with prostate cancer and 368 age-matched controls. In this study, men with high grade and/or high stage prostate cancer had a statistically significant higher proportion of short CAG repeats. In addition, initial observations in prostate cancer patients suggested an inverse relationship between CAG repeat length and cancer progression. *(29, 30)* These studies, although preliminary, are

the first to link a specific germline genomic polymorphism and prostate cancer risk. The implications of these studies are far reaching. The ability to stratify men according to prostate cancer risk using a simple genomic test could potentially alter current approaches to prostate cancer screening and/or prevention efforts.

a. CAG Repeat Length and Ethnic/Racial Differences

The CAG repeat length in the population is highly polymorphic. African-American males have a population average of 20.1 repeats, while caucasians average 22.0 repeats. Asians have a population average of 22.4 repeats. *(26)* Irvine et al. determined that the CAG repeat length is highly correlated with race and the frequency of prostate cancer within a population. *(31)* The prevalence of short repeat lengths (< 22) was highest (75%) in African-Americans, the group with the greatest risk for prostate cancer. Asians have the lowest risk of developing prostate cancer and the lowest prevalence of short CAG repeat lengths (49%). Non-Hispanic whites have an intermediate risk and a prevalence of 62% for < 22 CAG repeats.

b. CAG Repeat Length and Age of Onset

Many of the studies that have studied CAG repeat length have attempted to demonstrate a correlation with age of onset of the disease. Hardy et al. analyzed 109 men with histologically confirmed prostate cancer and found a positive correlation between shorter CAG repeat lengths (22 repeats) and younger age at diagnosis. *(28)* Stanford and colleagues also found that among men under the age of 60 years, there was shorter CAG repeat length and an increased risk of prostate cancer. However, in men between the ages of 60 - 64 years, shorter repeat lengths did not correlate with an elevated risk. *(27)*

c. CAG Repeat Length and Family History

Men with a family history of prostate cancer are at an increased risk of developing prostate cancer. Stanford et al. recently analyzed the CAG repeat length in 301 caucasian prostate cancer patients and 277 age/race-matched controls. *(27)* In this study, no association was found in men with no family history. Among men with either a father or brother affected with the disease, there was an increased risk associated with a shorter CAG repeat length (< 22 repeats).

3.0 STATISTICAL CONSIDERATIONS

3.1 Introduction: The primary objective of this study (Section 1.1) and the secondary modeling objective (Section 1.2.1) cannot be analyzed until the clinical study is completed. The Data and Safety Monitoring Committee will not release data on incident cases discovered prior to the biopsy period, and full statistical power will not be available until all cases have been identified.

It is anticipated that there will be approximately 600 prostate cancer cases among the men randomized to the PCPT. Some of these cases will be identified prior to the scheduled biopsy. All 600 cases will have CAG repeat length assays. A sample of 1,200 controls (non-cases) will be identified and have CAG repeat length assays. Controls will either be

randomly selected from among men who have no evidence of prostate cancer, or be obtained using matching criteria. Potential matching factors include treatment arm, age at the time of randomization, and time on study. Consideration will also be given to using PSA level (adjusted PSA levels for finasteride arm patients) nearest to the time on study for the case as an additional matching factor for one of the controls. Higher PSA levels in controls may indicate the presence of undetected prostate cancer. Therefore, if CAG repeat length differences are smaller for the PSA matched controls then this would provide valuable additional information.

As implied in the previous paragraph, a significant methodological issue is that the existence of prostate cancer in cases will be known with high accuracy, whereas the absence of prostate cancer in controls is only presumed. This potential for misclassification in controls means that the results will have to be interpreted with caution, and innovations may be necessary (such as the PSA matching described above) in order to attempt to overcome the impact of this misclassification potential.

3.2 Objective 1.1: A sample size of 600 cases and 1,200 controls provides exquisite power for comparing the mean CAG repeat lengths between cases and controls. The standard deviation of CAG repeat length measurements is generally about 3.1. For the use of a *t* test for difference in the mean CAG repeat length between cases and controls, it is computed that as small as a 0.5 unit difference is detectable with a two-sided type I error probability of 0.05 and type II error probability of 0.1.

3.3 Objective 1.2a: The anticipated sample size should be adequate for most statistical modeling activities. All statistical modeling will be carried out in an exploratory mode and using standard protections against overfitting and overinterpretation. The primary modeling methodology will be logistic regression with the case/control status as the outcome and the explanatory variables mentioned in Section 1.2a as explanatory variables. The primary assessment will be to ascertain whether the CAG repeat length variable is additive to the other explanatory variables, including interactions where appropriate. In addition to logistic regression, more exploratory methods, such as regression trees, will be used.

3.4 Objective 1.2b: The analyses associated with secondary Objective 1.2b can be begun immediately because cancer incidence outcome will not be used. There will be an attempt to obtain results from 150 specimens for each ethnic or racial group. For the unadjusted comparison of CAG repeat length between two groups, under the conditions specified above to compute the sensitivity for the primary objective it is found that a CAG repeat length difference as small as 1.6 units is detectable. This is smaller than the previously reported differences between African-Americans and caucasians.

3.5 Objective 1.2c: The analyses associated with secondary Objective 1.2c can be begun immediately because cancer incidence outcome will not be used. There will be an attempt to obtain results from 500 specimens from those with a positive family history of prostate cancer and 500 controls (race matched) without a family history. For the unadjusted comparison of CAG repeat length between two groups under the conditions specified above to compute the sensitivity for the primary objective, it is found that a CAG repeat length difference as small as 0.6 units is detectable.

3.6 Data flow: The specimens will be identified at the Southwest Oncology Group Statistical Center, after which the tubes, labeled with accession number, will be shipped to Dr. Figg's laboratory (address listed below) for CAG repeat length assay. The results of each

assay identified with the patient number will be transmitted to the Southwest Oncology Group Statistical Center for analysis according to the stated objectives. The PCPT data base will be used as the source of outcome and other explanatory variables for the analyses.

4.0 METHODS

4.1 DNA Isolation from Frozen Serum

Serum samples have been collected from all patients enrolled in the PCPT. Frozen serum in 1 mL aliquots will be shipped from the Central Laboratory Facility to Dr. William D. Figg at the National Cancer Institute. The NCI Intramural Program will pay for FEDEX shipping. The samples will be shipped on dry ice for next day delivery (only ship on Monday, Tuesday, or Wednesday). Upon arrival, the samples will be cataloged and stored at -85°C. Efforts will be made to minimize the time unfrozen. At the time of DNA isolation, serum samples will be rapidly thawed and aliquoted into 200 µL volumes and immediately refrozen, except for the aliquot to be used for extraction, in a dry ice/ethanol bath. Extraction of genomic DNA for the amplification of the CAG repeat region has recently been validated by Sartor and Zheng. *(32)* Genomic DNA is extracted from 200 µL of serum using either a QIAamp® blood kit (Qiagen, Chatsworth, CA) or Easy-DNA™ (Invitrogen, San Diego, CA). Both of these protocols have been modified and optimized for extraction of DNA from serum. Long term storage of DNA is at -85°C.

4.2 Amplification of the CAG Repeat Region of the Androgen Receptor

Polymerase chain reaction (PCR) is performed on ~50 ng of DNA in the presence of 50 mM TrisHCl, pH 8.3 (25%C), 2.0 mM $MgCl_2$, 0.25 mg/ml bovine serum albumin, 0.5% (w/v) Ficoll 400, 1.0 mM tartrazine, 375 µM of each dNTP, 1.25 µM of each primer, and 0.4 units *Taq* DNA polymerase (Perkin-Elmer, Foster City, CA) in a total volume of 10 µl. The primers, synthesized by BioServe Biotechnologies (Olney, MD), are similar to those previously reported by Barrack and colleagues for amplification of the region in exon A of the androgen receptor containing the CAG repeat region. *(33)* The primer sequences are as follows: 5'-TCCAGAATCTGTTCCAGAGCGTGC-3' (sense) and 5'-GCTGTGAAGGTTGCTGTTCCTCAT-3' (antisense). The PCR amplification parameters are an initial cycle at 95%C for 1 minute followed by 34 cycles of five seconds at 95%C, zero seconds at 55%C and 20 seconds at 72%C with a sloping parameter of 9.9. A single cycle at 72%C for 30 seconds concludes the PCR. All PCR is performed in a Rapidcycler (Idaho Technologies, Idaho Falls, ID) using 10 µL glass capillary tubes. Each DNA will be amplified two times.

4.3 Gel Analysis of Amplified Fragments

The PCR reaction is diluted with 4 µL DNA Sequencing Stop Solution (10 mM NaOH, 95% (v/v) formamide, 0.05% (w/v) bromophenol blue, 0.05% (w/v) xylene cyanol) and denatured at 70%C for 2 minutes. An aliquot, 3.5 µL, of each reaction is separated on a 6% polyacrylamide, 7 M urea, Tris-borate-EDTA (0.09 M Tris-borate, 1 mM EDTA, pH 8.3) gel at 55%C (~80W). On each gel, a control sequencing reaction of pCR-Script™ SK(+) amp^R plasmid (Stratagene, San Diego, CA) primed with M13 forward primer (Bioserve Biotechnologies, Olney, MD) is run. The control sequencing reaction is prepared using the SILVER SEQUENCE™ DNA sequencing system (Promega, Madison, WI). DNA is detected using the SILVER SEQUENCE™ DNA staining kit (Promega, Madison, WI).

Each DNA will be analyzed twice. Fragment size is determined by aligning it with the known sequence of the pCR-Script™ control plasmid. The number of base pairs in the fragment will be the same as the number of base pairs sequenced in the control plasmid at the alignment point. The number of CAG repeats are calculated by subtracting the known sequence flanking the CAG repeat region from the total fragment size.

4.4 DNA Sequencing of PCR Products

As a quality assurance of the PCR, one out of every twenty PCR fragments amplified will be sequenced using the ThermoSequenase cycle sequencing kit (Amersham, Cleveland, OH) according to the manufacturer's directions. Any amplifications producing multiple or ambiguously sized bands upon gel analysis will also be sequenced. Sequencing will done for both DNA strands in duplicate using a set of primers that anneal internally to the initial PCR primers. The nested primer sequences are: 5'-GCGAAGTGATCCAGAACCCGG-3' (sense) and 5'-CCAGGACCAGGTAGCCTGTGG-3'.

4.5 Contamination Control of DNA and PCR Reagents

The possible contamination of DNA and PCR reagents will be controlled by amplifying an unrelated gene that also contains a polymorphic CAG repeat region, SCA1, for every 20 samples analyzed or any DNA that displays ambiguous results. SCA1 is the gene associated with spinocerebellar ataxia type 1 and has been localized to human chromosome 6p22-23. *(34)* The PCR conditions for this gene uses ~75 ng of DNA in a reaction mixture of 50 mM TrisHCl, pH 8.3, 3 mM $MgCl_2$, 0.25 mg/mL bovine serum albumin, 0.5% (w/v) Ficoll 400, 1 mM tartrazine, 375 µM each dNTP, 1.5 µM of each primer, and 0.5 units *Taq* DNA polymerase (Perkin-Elmer, Foster City, CA) in a total volume of 10 µL. The PCR sequences were taken from Zoghbi et al. and are as follows: 5'ACCGCCAACCCCGTCACC-3' (sense) and 5'-GCTCTTCTCCATCTCACCGT-3'. The optimal cycling parameters involve an initial denaturation at 95%C for 45 seconds followed by 35 cycles of 93%C for 4 seconds, annealing at 60%C for 6 seconds, and extension at 72%C for 20 seconds with a sloping parameter of 9.9. A final extension at 72%C for 30 seconds concludes the PCR. The reactions are prepared and analyzed in the same fashion as for androgen receptor CAG repeat region.

All reactions are prepared in an OMNI PCR workstation (Astec Microflow, Fort Myers, FL) that has been decontaminated by ultraviolet irradiation for at least 15 minutes prior to use and has certified Class II laminar flow. The workstation and all pipette barrels are irradiated with ultraviolet light for 2 hours. Additional safeguards include the use of presterilized, aerosol free pipette tips and microfuge tubes for all operations. A single technician has been dedicated to cataloging and aliquoting all sera and extracted DNA. Another technician is responsible for the preparation of PCR and sequencing reagents.

4.6 Preliminary Results

Using the current method of DNA isolation, we can obtain 140-1000 ng DNA from 200 µL serum with an A_{260}:A_{280} ratio of 1.3 - 1.6. Of the patient sera we have examined to date, 29% had no detectable amplification products by ethidium bromide staining of the gels. Reactions that were negative for a product by ethidium bromide staining were reevaluated by staining with SYBR Green I (Molecular Probes, Eugene, OR). Using this stain, approximately 30% of the products that were previously undetectable were now easily seen. When products are run on denaturing gels and detected by silver staining, the yield is comparable to the SYBR Green I stain. Thus, the total recovery is 91%. In addition, we have not detected any artifacts that might be due to cross-contamination of DNA or reagents.

5.0 LITERATURE CITED

1. Wingo PA, Tong T, Bolden S. Cancer Statistics. CA Cancer J Clin 45:8-30, 1995.

2. Clayton LA, Byrd WM. The African-American cancer crisis, part I: The problem. J Health Care Poor Underserved 4:83-101, 1993.

3. Boring CC, Squires TS, Tong T. Cancer Statistics. CA Cancer J Clin 43:7-26, 1993.

4. Ndubuisi SC, Kofie VY, Andoh JY, Schwartz EM. Black-white differences in the stage at presentation of prostate cancer in the District of Columbia. Urology 46:71-77, 1995.

5. Mettlin CJ, Murphy G. The National Cancer Data Base report of prostate cancer [see comments]. Cancer 74:1640-1648, 1994.

6. Jones GW, Mettlin C, Murphy GP, Guinan P, Herr HW, Hussey DH, Chmiel JS, Fremgen AM, Clive RE, Zuber-Ocwieja KE, et al. Patterns of care for carcinoma of the prostate gland: results of a national survey of 1984 and 1990. J Am Coll Surg 180 (5):545-554, 1995.

7. Powell IJ, Schwartz K, Hussain M. Removal of the financial barrier to health care: does it impact on prostate cancer at presentation and survival? A comparative study between black and white men in a Veterans Affairs system. Urology 46:825-30, 1995.

8. Schapira MM, McAuliffe TL, Nattinger AB. Treatment of localized prostate cancer in African-American compared with Caucasian men. Less use of aggressive therapy for comparable disease. Med Care 33:1079-1088, 1995.

9. Moul JW, Sesterhenn IA, Connelly RR, Douglas T, Srivastava S, Mostofi FK, McLeod DG. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. JAMA 274(16):1277-1281, 1995.

10. Young CYF, Montgomery BT, Andrews PE, Qui S, Bilhartz DL, Tindall DJ. Hormonal regulation of prostate-specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. Cancer Res 51:3748-3752, 1991.

11. Kraus WL, McInerney EM, Katzenellenbogen BS. Ligand-dependent, transcriptionally productive association of the amino- and carboxyl-terminal regions of a steroid hormone nuclear receptor. Proc Natl Acad Sci USA 92:12314-12318, 1995.

12. Rundlett SE, Wu XP, Miesfeld RL. Functional characterization of the androgen receptor confirm that the molecular basis of androgen action is transcriptional regulation. Mol Endocrinol 4:708-714, 1990.

13. Kemppainen JA, Lane MV, Sar M, Wilson EM. Androgen receptor phosphorylation, turnover, nuclear transport, and transcriptional activation. Specificity for steroids and antihormones. J Biol Chem 267:968-974, 1992.

14. Zhou Z, Lane MV, Kemppainen JA, Wilson EM. Identification of three proline-directed phosphorylation sites in the human androgen receptor. Mol Endocrinol 9:605-615, 1995.

15. MacLean HE, Warne GL, Zajac JD. Defects of androgen receptor function: from sex reversal to motor neurone disease. Mol Cell Endocringol 1995;112:133-41.

16. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effects of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1:293-297, 1941.

17. Beato M. Gene regulation by steroid hormones. Cell 56:335-344, 1989.

18. Kyprianou N, English HF, Isaacs JT. Programmed cell death during regression of PC-82 human prostate cancer following androgen ablation. Cancer Res 50:3748-3758, 1990.

19. Chang C, Kokontis J, Liao S. Molecular cloning of human and rat complementary DNA encoding androgen receptors. Science 240:324-326, 1988.

20. Edwards A, Hammond H A, Jin L, Caskey CT, Chakraborty R. Genetic variation at five trimeric and tetrametric tandem repeat loci in four human populations. Genomics 12:241-253, 1992.

21. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen gene mutations in X-linked spinal and bulbar atrophy. Nature 352:77-79, 1991.

22. Sobue G, Doyu M, Morishimi T, Mukai E, Yasuda T, Kachi T, Mitsuma T. Abberant androgen action and increased size of the tandem CAG repeat in androgen receptor gene in X-linked recessive bulbospinal neuropathy. J Neuro Sci 121:167-171, 1994.

23. Mhatre AN, Trifiro MA, Kaufman M, Kazema-Esfarjani P, Figlewicz D, Rouleau G, Pinsky P. Reduced transcriptional regulatory competence of the androgen receptor in X-linked spinal and bulbar muscular atrophy. Nature Genetics 5:184-187, 1993.

24. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nuc Acids Res 22:3181-3186, 1994.

25. Scher H, Hardy DO, Bogenreider T, Amsterdam A, Frank K, Zhang ZF, Catterall J, Nanus D. Androgen receptor CAG repeat length polymorphisms in patients with prostate cancer: association with sensitivity to androgen ablation. Proc Am Soc Clin Oncol 14:232, 1995. (Abstr)

26. Coetzee GA, Ross RK. Prostate cancer and the androgen receptor. J Natl Cancer Inst 86:872-873, 1994.

27. Stanford JL, Just JJ, Gibbs M, Wicklund KG, Neal CL, Blumenstein BA, Ostrander EA. Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. Cancer Res 57:1194-1198, 1997.

28. Hardy DO, Scher HI, Bogenreider T, Sabbatini P, Zhang Z-F, Nanus DM, Catterall JF. Androgen receptor CAG repeat lengths in prostate cancer: correlation with age of onset. J Clin Endocrinol Metab 81(12):4400-4405, 1997.

29. Giovannucci E, Stampfer M, Krithivas K, Brown M, Talcott, Hennekens C, Kantoff P. The CAG repeat contained within the androgen receptor is a heritable factor that influences the clinical behavior of prostate cancer. Proc Am Soc Clin Oncol 15:252,1996. (abstr 646)

30. Giovannucci E, Stampfer MJ, Krithivas K, Brown M, Brufsky A, Talcott J, Henneken CH, Kantoff PW. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc Natl Acad Sci USA 94:3320-3323, 1997.

31. Irvine RA, Yu MC, Ross RK, Coetzee GA. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. Cancer Res 55:1937-1940, 1995

32. Sartor O, Zheng Q. Determination of CAG Repeat Length in the Androgen-Receptor Gene Using Frozen Serum. Urology 49(2):301-304, 1997.

33. Schoenberg MP, Hakimi JM, Wang S, Bova GS, Epstein JI, Fischbeck KH, Isaacs WB, Walsh PC, Barrack ER. Microsatellite mutation (CAG24 > 18) in the androgen receptor gene in human prostate cancer. Biochem Biophys Res Comm 198:74-80, 1994.

34. Zoghbi HY, Jodice C, Sandkuiji LA, Kwiatkowski Jr TJ, McCall AE, Huntoon SA, Lulli P, Spadaro M, Litt M, Cann HM, Frontali M, Terrenato L. The gene for autosomal dominant spinocerebellar ataxia (SCA1) maps telomeric to HLA complex and is closely linked to the D6S89 locus in three kindreds. Am J Hum Genet 49:23-30, 1991.

Appendix 19.9

White Blood Cell and Plasma Collection Procedures

1.0 OBJECTIVES

1.1 To provide a resource for studies of early markers, etiology, and genetic risk factors for prostate cancer and other diseases.

2.0 BACKGROUND

The Prostate Cancer Prevention Trial (PCPT) is a randomized double blind chemoprevention trial designed to test the difference in the histologically-proven prostate cancer prevalence between a group of participants taking finasteride and another taking placebo for seven years. At randomization, participants were age 55 or older with a normal DRE, no severe prostatism, a PSA ≤ 3 ng/ml and no prostate cancer or PIN. Participants are treated for a total of seven years with either finasteride or placebo and followed annually with a DRE and PSA. At the end of seven years, each living participant not previously diagnosed with prostate cancer will have a prostate biopsy to assess the presence or absence of prostate cancer.

Initial blood collection was specifically for the analysis of PSA and storage of serum. However, the size of this cohort provides an ideal opportunity to carry out additional research into the environmental and genetic factors which influence risk for development of prostate cancer. Some of these studies could make use of plasma and white blood cells which are not currently available from study participants. Thus, an additional blood collection will be carried out using anticoagulant so that plasma and white blood cells can be isolated. Plasma will allow the analysis of additional biomarkers such as albumin adducts, while white blood cells will provide a source of DNA. This DNA will be used (among other possible uses) for studies to investigate polymorphisms in genes which may influence prostate cancer risk. For example, interindividual differences in carcinogen or hormone metabolism, related to polymorphisms in specific genes, can be determined by polymerase chain reaction-restriction fragment length polymorphism analysis of DNA. Similarly, polymorphisms in genes responsible for detoxification of carcinogens or DNA repair can also be analyzed.

This appendix is intended to provide the rationale and procedures for the additional voluntary submission of white blood cells for future analyses. These samples, as well as the serums for annual PSA analysis and banking and tissue from all prostate procedures, are an invaluable resource for investigations into cancer etiology and prevention.

The PCPT WBC sample will be available to PCPT investigators as well as outside researchers who have important, timely hypotheses to test. Because the sample bank is a limited resource, proposals to use it will be evaluated in terms of scientific relevance, significance, and validity as well as the potential impact of the proposed study. The amount and type of material needed will also be considered and the efficient use of material will be required. Strict confidentiality will be exercised and the information provided to investigators will not contain personal identifiers.

When specific uses of the WBC samples are approved, the **SWOG-9217** protocol will be amended.

Participation in this research is not required for continued participation in the PCPT.

3.0 METHODS

3.1 Because the original model consent form did not specifically address genetic studies, participants will be asked to sign an additional consent form to document their consent to the collection and submission of additional blood samples for storage and future testing (including genetic analysis).

3.2 Institutions will be asked to submit additional materials from participants who consent to the additional blood collection. The blood is to be collected, processed and shipped as described in the PCPT Study Manual.

3.3 NCI-Frederick Cancer Research Development Center (FCRDC) in Frederick, Maryland will serve as the processing, aliquotting and storage facility.

3.4 Upon arrival at FCRDC the blood will be pooled and centrifuged. Plasma will be separated into 5 x 1.8 ml aliquots and frozen at -70°C. Buffy coat white blood cells will be collected and separated into two aliquots: an aliquot consisting of about 90% of the cells will be frozen for later DNA extraction (vapor-phase liquid nitrogen). The remainder of the WBC cells will be stored in freezing media containing DMSO for the preservation of viable cells in duplicate 0.5ml aliquots (also in liquid nitrogen). This will permit future transformation of lymphocytes and establishment of cell lines.

3.5 All samples will be logged in and aliquots will be bar coded with a unique storage ID. These data will be electronically transmitted to the Statistical Center for verification.

3.6 The scientists who will carry out analyses on these materials will not have access to personal identifiers and will not be able to link the results of these tests to personal identifier information. No individual results will be presented in publications or other reports. It will only be possible to link test results with past and future test results and the clinical data through the participant ID/storage ID link.

3.7 Participants will not be informed on an individual basis of any results from these studies. All reporting will be on a group basis only, without identification of individual test results.

4.0 SAMPLE ANALYSIS

4.1 Investigators planning to submit NIH grant applications must obtain approval for their study and specimen access from the PCPT Serum and Tissue Utilization Committee before submission of a grant proposal. Potential investigators will be required to submit a brief abstract and 1 - 4 page outline of the background, hypothesis, methods and statistical analysis plan as well as their NIH formatted biographical sketch and current support. This proposal will be circulated for review to members of the PCPT Serum and Tissue Utilization Committee and two *ad hoc* members having relevant expertise in cancer genetics and molecular biology and who are not affiliated with Southwest Oncology Group.

4.2 It is anticipated that proposals will be reviewed once a year. In this way multiple requests can be coordinated and dealt with in an efficient and prioritized manner. Approval by this group as well as appropriate Institutional Review Board approval from the investigator's institution will be required before release of samples.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	Flesch Reading Ease	49.0 (targeted above 55)
	Flesch-Kincaid Grade Level	10.6 (targeted below 8.5)

SWOG-9217, "Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III."
-Collection and Storage of White Blood Cells and Plasma for Additional Biologic Studies

This is a clinical trial (a type of research study). Clinical trials include only people who choose to take part. Please take your time to make your decision. Discuss it with your family and friends.

WHY IS THIS STUDY BEING DONE?

The purpose of the Prostate Cancer Prevention Trial (PCPT), in which you are currently participating, is to determine if there is a difference in the occurrence of prostate cancer between a group of healthy men who received finasteride and a group of healthy men who received a placebo.

The Prostate Cancer Prevention Trial also seeks to identify factors which may cause prostate cancer to develop and progress. Additional research on cancer and other diseases which occur in your age group will be carried out among Prostate Cancer Prevention Trial participants who volunteer to have a blood sample sent to a storage facility to be used for these additional studies. We are requesting your consent to participate in these additional studies of cancer and other diseases that occur in your age group.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Submission of this blood sample is optional. All of the PCPT participants may take part in this study regardless of whether they are currently taking study drug.

WHAT IS INVOLVED IN THE STUDY?

If you volunteer for these additional studies, additional blood will be drawn for use in future medical research. The blood samples will be labeled with a code number, so that researchers can obtain clinical information about the person from whom the sample came. The list of code numbers will be kept separately. Your name will not be revealed to researchers doing studies on the blood samples. This blood will be reserved for studies to determine if genetic (inherited) factors or chemicals in blood, such as dietary nutrients or hormones, are related to the risk of developing cancer and other diseases that occur in your age range. Additional health-related information about you may also be provided to researchers to help in this work. The blood samples collected will be stored at the Southwest Oncology Group research storage facility for up to 25 years and used to help scientists learn what causes cancer and how to prevent its progression. Therefore, the samples of blood which you contribute may be used in biochemical and genetic studies to identify these possible causes.

HOW LONG WILL I BE IN THE STUDY?

This part of the study will take only a few minutes to draw the blood sample. As mentioned above, the material will be stored at the storage facility for up to 25 years.

WHAT ABOUT CONFIDENTIALITY?

The information concerning your participation in this study will be kept confidential and used only for scientific purposes, in accordance with applicable state and federal laws. As genetic research may discover genetic information about you, this information will be kept confidential to the full extent permitted by law. Your blood and health information will not be labeled with your name and no one who works with these samples will have access to that information. Your name and any identifying information will not be used in any reports.

The blood samples that will be available to researchers will be identified with a code number. A file linking the code number with your name will be kept separately. If a researcher wants clinical information about you, she/he will ask for it by code number, but will not be able to know your name or other identifying information.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute, the Food and Drug Administration and the Southwest Oncology Group.

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

WHAT ARE THE RISKS OF THE STUDY?

The greatest risk to you is the release of information from your health record. As indicated elsewhere in this consent form, identifying information (which includes your name, address, and phone number) will be taken off anything associated with this blood sample before it is given to the researcher. This will make it very difficult for any research results to be linked to you or our family. There is always a remote risk that information from your health record would adversely affect applications for insurance or employment of you or other members of your family. The Southwest Oncology Group is in charge of making sure that this will not occur as a result of any research using your blood sample and that information about you is kept private.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

The additional studies will not provide direct benefit to you other than the satisfaction of participating in this research for the possible benefit of future generations. However, your participation in these additional studies may help answer questions related to the health and longevity of persons in your age group and may help establish a scientific understanding of the factors which influence the development and progression of cancer.

WHAT ARE THE COSTS?

The additional blood samples are for medical research only and the research results are not suitable for use as clinical tests for your medical care. The scientific studies require only looking at all lab results together. Therefore, the results of these additional studies will not be available to you. The blood samples will only be used for research and will not be sold. If any new scientific or medical testing products are developed using the results of the research done on your samples, you will not be paid, even if these medical products are sold.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds/funds have been set aside to compensate you in the event of injury. *(local institutions must choose the option that best fits the hospital's situation)*

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

As a participant in the Prostate Cancer Prevention Trial, you will be contributing to an important scientific investigation and will be notified about important scientific findings of these studies. This notification will be of results for all participants together. No individual results will be provided from these tests.

Your participation in the additional medical research is voluntary and you may refuse to participant and/or withdraw your consent and discontinue participation at any time without penalty or loss of benefits to which you are entitled.

You may participate in the Prostate Cancer Prevention Trial and yet decline to have these additional blood samples stored for research purposes. Further, if you initially decide to have your biologic samples stored for research purposes, but later change your mind by written notification of **(principal investigator)** at the **(participating institution)**, whatever remains of your biologic samples will then be destroyed. Your decision will not affect your care.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher _ *NAME(S)* _ at _ *TELEPHONE NUMBER* _.

For questions about your rights as a research participant, contact the _ *NAME OF CENTER* _ Institutional Review Board (which is a group of people who review the research to protect your rights) at _ *TELEPHONE NUMBER* _. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources]

You may call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Visit the NCI's Web sites…
cancerTrials: comprehensive clinical trials information http://cancertrials.nci.nih.gov.

CancerNet™: accurate cancer information including PDQ
http://cancernet.nci.nih.gov.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.
My signature below means that I freely agree to participate in this additional medical research. **My consent to participate in the Prostate Cancer Prevention Trial has been provided in a separate document**.

By signing this consent, I agree to have biologic samples (some of my blood) stored for **future research on cancer and other diseases that effect my age group**. I understand that it may involve genetic and biochemical studies.

Participant _____ Date _____

Appendix 19.10

Extended Follow-Up

1.0 OBJECTIVES

The extension of the PCPT will continue follow-up of the participants in PCPT through 2005. This will provide 10 years of continuous observation for the majority of subjects randomized on the trial to meet the following objectives:

- Monitor prostate cancer incidence to determine if, with longer follow-up, a difference in prostate cancer incidence rates between finasteride and placebo emerge.
- Monitor mortality due to all causes to strengthen mortality comparisons performed at the end of the original trial.
- Assess long term side effects to evaluate the impact of prolonged finasteride use on general well being and urologic symptoms within the years following cessation of use.
- Establish and retain a cohort of participants for long-term follow-up within the framework of a Southwest Oncology Group study to assess long-term differences in prostate cancer-specific mortality in the two arms of the study.

2.0 BACKGROUND

In January 2001, the first of the men who were randomized on PCPT will undergo their end of study biopsies. During the period between early 2001 and mid-2004 (seven years after the last man was randomized) all men who have not previously been diagnosed with prostate cancer will have end of study biopsies scheduled. Under the current study design, the end of study biopsy is the termination point for follow-up. Participants who refuse the end of study biopsy are to have their follow-up terminated at the date of their final annual visit, seven years after their entry to the trial.

Incidence analysis

When the PCPT was designed, several biases were anticipated that could affect the trial results. For example, the knowledge that finasteride could alter PSA levels led to concerns about PSA detecting cancers differentially in the two arms of the study. The decision to perform an end of study biopsy reflected the belief that a sextant biopsy of the prostate, performed after seven years of the trial, would be the least biased measure of disease prevalence in the two arms of the study. Additionally, it was anticipated that a sextant biopsy of a gland treated with finasteride would also *oversample* the gland as (1) finasteride causes an about one-third reduction in gland volume and (2) the needle would then traverse a proportionately higher proportion of the gland. It was felt that this potential bias against finasteride would result in any perceived effects of finasteride being even more clinically significant.

A group of urologic investigators (Thompson, Klein, Presti) recently conducted a review of potential methods to change the manner of prostate biopsy for the end of the PCPT. Four options were discussed: (1) adjusting the number of cores based on prostate volume, thus ensuring equal sampling of prostates; (2) increasing the number of cores performed for each end-of-study biopsy to 10-12; (3) allowing investigator discretion on the number of cores obtained, and (4) maintaining the number of cores at six. Each of these methods has inherent problems and possible biases.

After evaluating the four possible options, the final choice was to retain the requirement of six cores. One advantage is that this is the number of cores the participant is expecting and the number to which he originally consented; thus a re-consent would not be required. Also, there is no bias introduced in favor of finasteride, and no changes in any of the study educational products (e.g., videos) would be required. However, after considerable discussion, it was decided that the best method to take into account this differential detection between the arms without creating a new ascertainment bias would be to change the biopsy technique. The suggested change in technique is to biopsy the prostate as much as possible from the peripheral zone of the gland. This can be accomplished by positioning the direction of the needle more laterally. As the principal volume shrinking effect of finasteride is on the transition zone of the gland, this lateral positioning increases the likelihood that the peripheral zone (the region of interest for prostate cancer diagnosis) is *equally sampled* in participants receiving finasteride or placebo.

It is readily apparent that, despite the decision that PCPT will continue to have sextant biopsies as a part of the study, there is a risk that the gland volume/tumor detection relationship may bias the study's conclusions against finasteride. As such, a potentially significant positive effect may not be detected by the current PCPT study design. If such a benefit did occur, it would be anticipated to emerge over the course of the life of the PCPT participants. By engaging in longterm follow-up we will be better able to address this issue of ascertainment bias.

Mortality analysis

The number of deaths expected during the design phase of the trial was 20%. Because of the pattern of accrual to the PCPT (64% in the first year), follow-up on all participants until 2005 will provide us with a considerable amount of additional data regarding deaths, including cause of death and the relationship of prostate cancer to death.

Long term side effects and urologic symptoms analysis

One of the secondary objectives of the PCPT was to assess the effect of long-term treatment with finasteride on the participants' self report of urinary symptoms. This extension would allow us to follow the participants to evaluate the impact of the prolonged use of finasteride on urologic symptoms and general well being following the cessation of use. Should the study be positive, these data are important to evaluate so future users of finasteride for the prevention of prostate cancer can be appropriately counseled as to the long-term effects.

Retention of cohort

During this extension, all participants will be offered continued annual follow-up. In this way, should a negative study result be encountered and it is determined that biopsy bias is operational, further evaluation of the study cohort can proceed. Moreover, this extended follow-up is vitally important should longer term follow-up be deemed necessary. Indeed, without such a study extension, there would be limited possibility of achieving long-term follow-up and of assessing disease-specific mortality. Contact with the majority of participants would have been lost and re-contact and re-enrollment in a long-term follow-up study would be difficult if not impossible.

3.0 STUDY DESIGN

All men who were randomized on the PCPT and who are not currently registered to another Southwest Oncology Group trial are eligible for enrollment to the extension of PCPT. This includes men for whom prostate cancer was diagnosed, those who had the end of study prostate biopsy and those who refuse the end-of-study prostate biopsy. Enrollment of participants in the extension will occur after the completion of seven years on study and the performance of the end-of-study biopsy (or the refusal). The participant will need to be counseled regarding the proposed study and an additional informed consent will be obtained.

Follow-up for participants enrolled on the extension of PCPT will be similar to Off Treatment follow-up on PCPT, with the exception of PSA testing, which will be done locally.

Participants who have not had a diagnosis of prostate cancer will be followed every six months. The preferred method of contact at the six-month contact will be by telephone; the preferred annual contact will be a Study Site visit. Follow-up will include:

- General Health questions including prostate events, finasteride use and assessment of potential long-term finasteride effects.
- A recommended, but not required, annual DRE and PSA performed locally (Study Site, primary care physician or other healthcare professional)
- Recommendation for a prostate biopsy based on al DRE that is suspicious for cancer or an elevated PSA (total PSA ≥ 4.0 ng/ml)

Participants who have had a diagnosis of prostate cancer will be followed annually for a general health and vital status update. Six-month contact for these participants will not be performed.

Detailed follow-up activities and procedures can be found in *Appendix L* of the PCPT Study Manual.

4.0 LENGTH OF THE EXTENSION STUDY

The final end of study biopsy will be performed in approximately May 2004 and complete ascertainment of prostate cancer diagnosis will not be final until mid-2004. It is anticipated that the final analysis of the PCPT will require several additional months. Should further follow-up of PCPT participants be appropriate or necessary, it is anticipated that a minimum of nine additional months will be required for protocol development, review, activation as well as consent. It is for this reason that this extension is planned through 2005.

Pathology

Central review of prostate cancers will not be necessary. However, each participating Study Site will be required to submit a copy of the pathology report to the Statistical Center when a prostate cancer case is diagnosed.

5.0 STATISTICAL CONSIDERATIONS

The analyses of prostate cancer incidence and all-cause mortality following this extension will be similar to those conducted at the end of the PCPT, but will be augmented by additional endpoint data collected during the extension.

Incidence

Incidence comparisons will be performed using a discrete life table approach where the intervals of observation will consist of the seven-year period of the initial study and each year thereafter for a maximum of ten years of follow-up for the men randomized in the first year of PCPT. The life table will therefore have four cells. Participants followed for the full ten years will contribute to all four cells. The life table approach is necessary because of the potentially reduced sample size for the short-term extension due to some participants refusing to enroll. Those who refuse will be censored at their exit from the PCPT. We will assume that PCPT participants who agree to continue with the short-term extension are representative of the population as a whole in terms of their future incidence of prostate cancer. To check this assumption we will carefully compare

participants who agree to continue with those who refuse in terms of their age, race, and other risk factors for prostate cancer e.g., the presence of high-grade PIN (prostatic intraepithelial neoplasia). Should evidence be found to violate this assumption we will conduct sensitivity analyses to evaluate the robustness of our results.

To compare cumulative incidence of prostate cancer in the control and intervention groups over the full period of observation, a two-sample test will be conducted at a significance level alpha=0.05. The test statistic will be given by:

TS = (S1-S2) / sqrt(var(S1)+var(S2)),

S1 and S2 are the estimates from the lifetable at the end of observation for the control and finasteride groups respectively, and var(S1) and var(S2) are their estimated variances.

It is difficult to project the number of additional prostate cancers that will be diagnosed during the short term extension since the incidence following a negative prostate biopsy with neither an elevated PSA nor an abnormal DRE is unknown. Data from the first three years of PCPT may be the best estimate. However, at this point, these data are not publicly available.

Mortality

To compare mortality in the control group with that in the intervention group, Kaplan-Meier curves with mortality as the endpoint will be constructed within each group. The curves will be compared using the logrank test at a significance level alpha=0.05. This analysis will assume that individuals agreeing to continue with the short-term extension are representative of the population in terms of their mortality risk. As a check of this assumption we will compare participants who agree to continue with those who refuse in terms of their age, presence of prostate or any other cancer and other co-morbidities where information is available.

For IRB use only, not to be included in patient information.

This model informed consent form has been reviewed by the DCP/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a participant may be registered to this study.

Readability Statistics:	Flesch Reading Ease	57.7 (targeted above 55)
	Flesch-Kincaid Grade Level	8.9 (targeted below 8.5)

SWOG-9217, "Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III."
Extended Follow-Up

This is a clinical trial (a type of research study). Clinical trials include only people who choose to take part. Please take your time to make your decision. Discuss it with your family and friends.

WHY IS THIS STUDY BEING DONE?

The purpose of the Prostate Cancer Prevention Trial (PCPT), in which you are currently taking part, is to find out if there is a difference in the occurrence of prostate cancer between a group of healthy men who received finasteride and a group of healthy men who received a placebo.

With an extension of your participation in this study, we hope to learn more about prostate cancer. We hope to stay in contact with you and collect extra data about the effects of finasteride use, prostate cancer and survival.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Taking part in this extension is your choice. All men taking part in PCPT may take part in this study regardless of whether or not they were taking study drug at the time of their final visit. They may take part whether or not they have been diagnosed with prostate cancer.

WHAT IS INVOLVED IN THE STUDY?

If you choose to take part in this extended study, you will continue being followed after the end of seven years on PCPT. Whether you choose to take finasteride during the extended study is up to you (this is not part of the extended study). *(8/15/01)* At a minimum, if you have a current or previous diagnosis of prostate cancer, taking part in the extension requires you to respond to a yearly telephone call asking for information about your health. *(8/15/01)*

Participants who do not have a current or previous diagnosis of prostate cancer will be contacted every six months. *(8/15/01)* You will have a phone contact midway through each year. You will also have an annual visit which may (if you choose) include PSA, DRE and will include general health questions. *(8/15/01)* A prostate biopsy may be recommended based on the PSA and DRE results.

HOW LONG WILL I BE IN THE STUDY?

We expect that this extension will last until May of 2005.

The researcher may decide to take you off this study if your health gets worse and the demands of the follow-up schedule are too difficult for you, or if new information about the study becomes available and this information suggests the extended follow-up would not be valuable. You may choose to withdraw from the study at any time for any reason. It is unlikely, but the study may be stopped early due to lack of funding. (paragraph added 8/15/01)

WHAT ABOUT CONFIDENTIALITY?

Information about your participation in this study will be kept confidential and used only for scientific purposes, in accordance with applicable state and federal laws. Your name and any identifying information will not be used in any reports.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute, the Food and Drug Administration, a qualified representative of the drug manufacturer and the Southwest Oncology Group.

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

WHAT ARE THE RISKS OF THE STUDY?

As a result of taking part in this extension, you may have PSA and DRE exams at your annual visits. Because of these tests, it is expected that early prostate tumors which otherwise would not have been found may be found in you or in other men on the study. Some of these tumors will be prostate cancer that needs treatment. It is also possible that tumors that do not need treatment may be found. At this time it is hard to tell the difference between these types of tumors. So, it is possible that you may receive unnecessary treatment that involves a real risk of side-effects. You and your doctor will decide the treatment that you will receive if prostate cancer is found during the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

The extra studies will not provide direct benefit to you other than the satisfaction of taking part in this research for the possible benefit of future generations. However, your participation in these extra studies may help answer questions related to the health and life span of persons in your age group. The study may help scientists understand things which influence the development and progression of cancer.

What Other Options Are There? (*question and paragraphs added 8/15/01)*

Instead of being in this study, you have these options:

You may participate in other prostate cancer prevention studies (including the SELECT - Selenium and Vitamin E Cancer Prevention Trial). If you are diagnosed with high grade PIN (prostate intrepithelial neoplasia), you may be eligible to participate in S9917, "L-Selenium-Based Chemoprevention of Prostate Cancer Among Men with High Grade Prostatic Intraepithelial Neoplasia".

There is no known way to prevent prostate cancer. You can choose to take finasteride, vitamins or other agents without being on this study.

Please talk to your regular doctor about these and other options.

WHAT ARE THE COSTS? *(moved from page 104 8/15/01)*

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds/funds have been set aside to compensate you in the event of injury. *(local institutions must choose the option that best fits the hospital's situation)*

Costs for the recommended annual DRE and/or PSA test will not be covered by this study. You or your insurance company will be billed for the cost of these tests. *(paragraph added 8/15/01)*

(Study Sites may choose to revise the preceding statement to better describe the process within the site.) (paragraph added 8/15/01)

You or your insurance company will be charged for continuing medical care and/or hospitalization. Specifically, you or your insurance company will be charged for any prostate biopsy recommended as part of the extended study. *(8/15/01)*

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

As a participant in the Prostate Cancer Prevention Trial, you will be contributing to an important scientific investigation and you have the right to be notified about important scientific findings related to this study. This notification will be of results for all participants together. No individual results will be provided.

Your participation in this extension is your choice and you may refuse to take part and/or withdraw your consent and discontinue participation at any time without penalty or loss of benefits to which you are entitled.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher _ *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *[And, if available, list participant representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources]

You may call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Visit the NCI's Web sites…
cancerTrials: comprehensive clinical trials information
http://cancertrials.nci.nih.gov.

CancerNet™: accurate cancer information including PDQ
http://cancernet.nci.nih.gov.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

Your signature below means that you freely agree to participate in this extended follow-up. **Your consent to participate in the Prostate Cancer Prevention Trial has been provided in a separate document**.

Participant _____ Date _____

Fact Sheet – PSA and DRE

Prostate cancer is the most common tumor in U.S. men. About one man in six born today will be found to have prostate cancer in their lifetime. It causes about 3 - 4% of all deaths to men in this country. While all men are at risk of developing prostate cancer, African Americans and those with a family history of prostate cancer are at a greater risk and may develop the disease earlier in life.

Often, prostate cancer is slow growing and may not be detected during a man's life or pose a risk to his health. In other men, spread can occur without symptoms. Generally, if cancer is detected because of symptoms, it has already spread and is incurable. While tumors confined to the prostate can usually be cured, once spread has occurred, most tumors cannot be cured.

Finding prostate cancer in a man with no symptoms is possible using two tests. One of these tests is the "digital rectal examination" (DRE), in which the doctor inserts a gloved finger into the rectum to feel for abnormalities on the prostate. The other test is the "Prostate Specific Antigen" (PSA) blood test, which can be higher than normal in men with prostate cancer. Using these two tests, doctors can find cancers at an early stage. If either test is not normal, the next step to find if prostate cancer is present is to pass a needle into the prostate to obtain tissue to study under a microscope. If cancer is found, additional blood tests and x-rays such as a bone scan or CAT scan may also be performed. Management of prostate cancer may include surgery, radiation, hormone treatments or watching and waiting, depending upon each individual's condition and choice. The best choice for a patient with prostate cancer is unknown. Men with this disease must weigh their choices and decide what is best for them.

There are no general guidelines for doing DRE and PSA. Many doctors do them once a year beginning at age 50. Participants in the PCPT Extended follow-up are recommended to have a DRE and PSA done yearly. Participants may do so because they or their doctor believes that yearly testing is good medical practice or simply as part of participating in the PCPT Extended follow-up. Participants may wish to talk to their regular doctor before having these tests performed.

There are good points and bad points to having regular DRE and PSA tests. The good points include: 1) most cancers diagnosed by these tests are curable, and 2) the tests are simple to perform and cause only minor pain. The bad points include: 1) only 1 in 4 men with an abnormal test actually has prostate cancer, which may lead to unnecessary worry about what an abnormal test means; 2) it is not known whether using these tests will save more lives; 3) some prostate cancers detected by these tests may be slow growing and do not need treatment; 4) some of the cancers detected by these tests are not curable; 5) treatment for prostate cancer by radiation or surgery can lead to side effects such as problems with urinary control, difficulty getting or maintaining an erection, and diarrhea or other rectal problems.

Men who participate in the PCPT Extended follow-up should learn about prostate cancer and the DRE and PSA tests. Resources to help make a decision include their regular doctors, the PCPT doctors and nurses, the American Cancer Society, the Cancer Information Service of the National Cancer Institute, and the American Urological Association. Some educational sources are listed below:

American Cancer Society (1-800-ACS-2345)
Main site: http://www.ca.cancer.org
The Prostate Cancer Resource Center: http://www3.cancer.org/cancerinfo/load_cont.asp?ct=36

Patient Data Query (National Cancer Institute)
Main site:http://www.nci.nih.gov
CancerNet Prostate cancer page: http://cancernet.nci.nih.gov/Cancer_Types/Prostate_Cancer.shtml

Cancer Information Service (sponsored by the National Cancer Institute)
Telephone: 1-800-4-CANCER

American Urological Association
Main site: http://www.auanet.org
Patient information: http://www.auanet.org/patient_info/index.cfm