SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distribution Date: December 14, 2009
DCP Submission: December 9, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

REVISION #3

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@cesmtp.ccf.org

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

REVISION #3

For those Study Sites whose Institutional Review Board (IRB) has not approved Amendment #5, the SELECT leadership has approved two alternative plans for presenting Centralized Follow-Up to participants, Plans B and C. Study Sites whose IRBs have not approved Amendment #5 should contact the SELECT Statistical Center to discuss these available options and to determine what additional materials are required for submission to the IRB. The appropriate plan for the Study Site will be based on the reasons provided by the local IRB for not approving Amendment #5. Plan B is the highly preferred alternate plan because it allows the participant to continue his participation on SELECT with the least additional effort. The study referenced above has been revised to insert Appendix 19.8 "Alternatives for Transition to Centralized Follow-Up (Plans B and C)".

Specific study changes related to this addition are outlined below:

1. The Version Date was updated on the face page.

2. A reference to Appendix 19.8 was added into Section 7.13 (Page 20) and to the appendix listing on Page 50.

3. Appendix 19.8 (Page 80) was added.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
DSM - Vishwa Singh, Ph.D. and James Elliott, M.D.
Perrigo - Mark Mincey
Tishcon - Arun Chopra
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. – RAS
M. Peter Lance, M.D. - ACP

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distribution Date: August 25, 2009
DCP Submission: August 14, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, S. Lucia, et al.

AMENDMENT #5

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

IRB Review Requirements

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

( ) Expedited review allowed

( ) No review required

AMENDMENT #5

As part of the process for streamlining efforts related to this study for the purpose of efficiency and cost-saving, we will be consolidating the future follow-up procedures for as many participants as possible.

The transition from local follow-up to centralized follow-up is planned to occur with the next scheduled participant follow-up visits beginning after November 1, 2009. These visits will be considered exit visits for the purposes of local institution follow-up responsibilities.

For participants who consent to centralized follow-up at the time of the SELECT transition visit, continued follow-up will be performed centrally by the SELECT Coordinating Center. For participants who refuse to consent to centralized follow-up, their participation in the SELECT study will end with the exit visit.

Please access the SELECT Workbench (particularly the Study Manual – Section 4.7, Transition Visit) to obtain detailed information regarding procedures for preparing for the transition visit. The transition visit itself will involve collection of additional data, unblinding, distribution of recognition items, obtaining consent for centralized follow-up and registering the participant to Registration Step 2 - **S0000** Centralized Follow-Up.

Please note the Study Multivitamins will be provided only as long as current supplies are available.

Specific edits associated with this amendment are as follows:

1. The Version Date on the Face Page has been updated. The table of contents was updated to reflect repagination.

2. A notation was added to Section 7.4 (Page 18) regarding discontinuation of the Study Multivitamin.

3. A notation was added to Section 7.5 (Page 19) regarding the transition to centralized follow-up.

4. A notation was added to Section 7.6c (Page 19) to indicate that specimen collection for adherence assessment ended in June 2009.

5. A notation was added into Section 7.12 (Page 20) indicating global unblinding will occur at the time of the participant's transition visit.

6. A new Section 7.13 was added (Pages 20 and 20a) to insert detail regarding the transition to centralized follow-up. Page 20b was added to prevent extensive repagination.

7. Columns were added to the Study Calendar (Page 21) for the Transition Visit and for Centralized Follow-Up. Rows were added for unblinding, obtaining consent for centralized follow-up and for participant report of medical events during centralized follow-up. Footnotes "α" and "y" were added.

8. A sentence was added to Section 12.1 (Page 25) to reference pathology data collection after transition to centralized follow-up.

9. A notation was added to Section 15.1 (Page 26) to indicate that blood will be collected at the Transition Visit for those participants who have been diagnosed with prostate cancer. Please use the Model Informed Consent – Collection and Storage of Additional Blood Specimens provided in Appendix 19.6 to develop your local consent form for this purpose.

10. Section 19.7 was added to provide an Informed Consent Form for Centralized Extension of Follow-Up. This is reflected on Page 50 and in the addition of Pages 74-79. By signing this consent form participants are agreeing to centralized follow-up and providing their contact information to the SELECT Coordinating Center. If participants choose not to sign this consent form, their participation in SELECT will end with their Transition Visit.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
DSM - Vishwa Singh, Ph.D. and James Elliott, M.D.
Perrigo - Mark Mincey
Tishcon - Arun Chopra
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. – RAS
M. Peter Lance, M.D. - ACP

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

August 25, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, S. Lucia, et al.

MEMORANDUM

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

IRB Review Requirements

( ) Full board review required

( ) Expedited review allowed

(√) No review required

MEMORANDUM

As a part of the process for streamlining efforts related to SELECT, we will be consolidating future follow-up procedures. The transition from local follow-up to centralized follow-up is planned to occur between November 1, 2009 and December 31, 2010.

There are several pieces of material related to this transition that will require local IRB review (for a summary of materials, see the Memorandum to Sites that is being sent to you and posted on the SELECT Workbench). We are asking that the IRB review this material in a timely manner so that participant transition visits will begin as soon as possible after November 1, 2009. The Southwest Oncology Group requires that IRB approval of Amendment #5 (attached) be submitted for entry into the database prior to approaching any participants with materials for the Transition Visit.

Please submit proof of IRB approval of Amendment #5 to:

Southwest Oncology Group Operations Office
Attn: IRB
14980 Omicron Drive
San Antonio, TX 78245
Phone: 210/450-8808
FAX: 210/677-0006

We encourage you to enclose the attached IRB Information Memorandum with the materials for local IRB review.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Ph.D. and James Elliott, M.D.
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons – PREADVISE
DSM - Vishwa Singh,
Perrigo - Mark Mincey
Tishcon - Arun Chopra
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. – RAS
M. Peter Lance, M.D. – ACP

IRB INFORMATION MEMORANDUM
for
S0000, Selenium and Vitamin E Cancer Prevention Trial (SELECT)
transition to centralized follow-up

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) ended intervention on October 23, 2008, after the study's definitive finding of no benefit from either supplement. Participants were quickly instructed to stop taking supplements but continue post-supplementation follow-up visits at our site. To streamline efforts related to SELECT, we will be consolidating future follow-up procedures. Participants will transition from local follow-up to centralized follow-up beginning after November 1, 2009 and prior to December 31, 2010.

By the time of the completion of the last Transition Visit at our site, we must have completed submission of all outstanding data, responded to data queries and performed all site closure tasks. At that time, the study will require no further IRB review at our site.

As a part of the Transition Visit, IRB responsibility for the follow-up of these participants will be switching from our institution to the IRB for Cancer Research And Biostatistics in Seattle, WA. The Cancer Research And Biostatistics IRB is responsible for the research activities of the SELECT Coordinating Center (which is part of the Southwest Oncology Group Statistical Center). We are asked to obtain participant consent on behalf of the study Principal Investigator for centralized follow-up activities Dr. John Crowley, and to FAX a copy of the last page (signature page) of the consent form to the SELECT Coordinating Center. We will then register the participant to Registration Step #2 of the study (no registrations to Step #2 will be accepted until the institution's IRB approval has been entered into the SWOG data base).

For each individual participant, our responsibility for institutional review ends with the Transition Visit and the participant's decision to either consent to centralized follow-up or not. If the participant chooses not to consent to centralized follow-up, his participation in SELECT and any of its substudies will end at that time. If he does consent to centralized follow-up, the participant will be registered to Step #2 of the protocol and institutional review responsibility will transfer to Cancer Research And Biostatistics at that time.

The Cancer Research And Biostatistics Institutional Review Board has already reviewed and approved the protocol amendment and all of the study transition materials. If you have questions about their review or their role in the transition of participants to centralized follow-up, please contact SELECT Project Manager Jo Ann Hartline at 206/839-1723.

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

June 23, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, S. Lucia, et al.

MEMORANDUM

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

IRB Review Requirements

( ) Full board review required

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The SELECT leadership has determined that collection and submission of blood samples for the serum-level adherence substudy will stop immediately. Sites participating in this substudy should not collect any more adherence samples. Protocol changes associated with this study change are planned to be distributed to sites in late summer. All future expectations for these samples will be deleted. A list of participating sites is available on the Ancillary Studies page on the SELECT Workbench.

Note: Collection of samples for the Additional Blood Draw will continue as described in **Study Manual Bulletin 12**.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
DSM - Vishwa Singh, Ph.D. and James Elliott, M.D.
Perrigo - Mark Mincey
Tishcon - Arun Chopra
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. – RAS
M. Peter Lance, M.D. – ACP

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distribution Date: November 18, 2008
DCP Submission: November 12, 2008

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, S. Lucia, et al.

AMENDMENT #4

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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 specimen banking requirements
(√) Study closure due to new information

( ) Expedited review allowed

( ) No review required

AMENDMENT #4

On September 15, 2008 the independent Data and Safety Monitoring Committee (DSMC) for SELECT met and recommended that participants stop taking their Study Supplements because the evidence to date convincingly demonstrated no benefit from either agent. Investigators from the study leadership and the National Cancer Institute have also reviewed the findings and agree with these recommendations. Participants are being informed of these findings and asked to discontinue taking the Study Supplements but continue with follow-up.

The review of data from the DSMC could not exclude the possibility that the Study Supplements might have latent effects and recommended continued monitoring of SELECT subjects to help clarify the effects of vitamin E and selenium. There is a possibility that vitamin E may contribute to an increased risk of prostate cancer and selenium may contribute to an increased risk of adult onset diabetes mellitus. Neither of these findings was statistically significant, but combined with the lack of benefit of the Study Supplements, the recommendation was to have participants stop taking Study Supplements. Continued follow-up may help to clarify the preliminary data.

Study transition documents (including a copy of the DSMC recommendations and copies of the participant notification letter) as well as other resources may be found at https://gill.crab.org/SELWBDocs/Transition/StudyTransition.pdf.

The study leadership determined that documentation of receipt of the Study Transition Letter would be sufficient and did not require participant re-consent. Therefore, the Model Informed Consent Form in the protocol has not been updated except to add information about the study's treatment stop date on page 37.

Additional changes include the following:

1. Contact information for the Study Coordinators has been updated as applicable on the face page and page 2. Dr. Lippman's telephone number was also updated in Section 8.1 (page 20). Dr. Janet Stanford was replaced with Dr. Regina Santella as the Study Coordinator for Molecular Epidemiology. The Version Date was also updated on the face page.

2. The treatment stop date was added to the study Schema on page 3, in Section 7.4 (page 18) and in Section 7.9b (page 20).

3. The reference to dispensing Study Supplements was deleted from and information regarding adherence and adverse assessment timing were added to Section 7.5 (page 19)

4. The timing of the additional blood draw for banking in Section 7.6e (page 19) and in the Study Calendar (page 21) was updated to reflect the request for expedited collection. The Study Calendar was also updated to delete the distribution of blinded Study Supplements. The "£" footnote on the Study Calendar was updated to include the information that supporting documentation for endpoints will be submitted to the Statistical Center upon request.

5. Participants will be unblinded upon request. New procedures for unblinding are now available and will be posted in the Study Manual. This change is reflected in Section 7.12 (page 20).

6. Section 16.0 was updated to acknowledge that pharmacies were sent Study Supplement destruction letters on 11/6/08, to update the Operation Office Serious Adverse Event (SAE) representative's phone number (page 26), as well as to include guidelines for SAE reporting during follow-up (page 28 and the addition of page 28a).

7. An editorial error was corrected on page 53.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
DSM - Vishwa Singh, Ph.D. and James Elliott, M.D.
Perrigo - Mark Mincey
Tishcon - Arun Chopra
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. – RAS
M. Peter Lance, M.D. - ACP

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distributed: December 22, 2005
DCP Re-Submission: November 21, 2005
DCP Submission: October 24, 2005

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, S. Lucia, et al.

AMENDMENT #3

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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 specimen banking requirements
( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

AMENDMENT #3

The study referenced above is being amended at this time to collect additional bloods from all SELECT participants for use in studies of prostate cancer risk and etiology as well as banking for future research. This is intended to support studies that will investigate the mechanisms and underlying effects of selenium and vitamin E supplementation on prostate cancer risk.

This amendment gives the rationale and procedures for additional, voluntary blood draws for SELECT participants. Currently, we plan to collect at least one post-randomization blood draw, the first at the 5 year (060) visit due to begin in July 2006. The timing of subsequent blood draws is not yet determined, however this protocol amendment also serves as notification to the sites that there may be future blood draws requested from SELECT participants. SELECT participants are not required to provide these additional blood samples, and they will continue as SELECT participants whether or not they decide to provide additional blood samples. If additional blood draws are requested, additional consent will also be requested from the participant at that time.

Participants will be asked to sign an informed consent amendment to document their consent to the collection, storage and future analysis of additional blood samples.

Study sites will be asked to obtain informed consent and to submit additional blood samples from consenting SELECT participants. The blood will be collected and shipped as described in the SELECT Study Manual.

Specific protocol changes associated with this amendment include the following: a paragraph was added to the end of Section 2.0 (page 10) to outline this activity – a new page 10a was added to prevent extensive repagination; a new Section 7.6e was added (page 19) and an "X" was added to the annual visit column on the Study Calendar (page 21) along with a footnote to add a reference to this procedure as part of the 5 year annual visit; Section 15.1 (page 26) was also amended to add a reference to blood collection at the 5 year annual visit.

The study Appendix was amended to add a new Appendix 19.6 – "Model Informed Consent – Collection and Storage of Additional Blood Specimens" (pages 70-73). By signing this new model informed consent form and agreeing to the blood draw and submission, participants are agreeing to the use of their blood specimens for correlative studies tied directly to the SELECT study. In addition, the participant's preferences for storage and future use of specimens will be as designated in the main SELECT consent form (and as outlined in the submitted Form 100 - Consent for SELECT Sub-Studies for each participant).

Additionally, the study has been amended to replace Dr. Wael A. Sakr with Dr. Scott Lucia as the pathologist for the study (face page). Mailing addresses and other contact information have also been corrected for the study statisticians, and for Dr. Alan Kristal and Dr. Janet Stanford (face page and page 2). Carol Moinpour, Ph.D. has been deleted as a QOL consultant. A new objective (Section 1.10, page 4) was added. The supplier information was corrected in Section 3.3c (page 12). A new "£" footnote was added to the Study Calendar (page 21) to remind Study Sites to collect and maintain supporting information for endpoint documentation in the participant's chart. The SAE reporting guidelines were revised (page 28) to correct an editorial error. A paragraph was added to the beginning of Appendix 19.2 to describe the clinical staging process for prostate cancer (page 51). References to the "Contact Database Project" have been deleted from the original Model Informed Consent Form (pages 39, 44, 45 and 46) as this project will no longer be a part of the SELECT study. Institutions are asked to inform their participants of this change as directed by the local IRB. Submission of Form 107 - Participant Address is no longer required.

Replacement pages are enclosed for the face page and pages 2, 4, 10, 12, 19, 21, 26, 28, 39, 44, 45, 46, 50 and 51. Please insert them into your copy of the protocol. Page 10a has been added to prevent extensive repagination and pages 70-73 have been added to incorporate the new consent form.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Perrigo - Mark Mincey
Tishcon - Arun Chopra
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE
Patricia A. Cassano, Ph.D. - RAS

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

March 26, 2004

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

STATUS REPORT

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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

STATUS REPORT

The above-referenced protocol has been permanently closed to randomization of participants **effective June 24, 2004.**

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
Perrigo - Mark Mincey
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

February 24, 2004

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

MEMORANDUM

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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

MEMORANDUM

This memorandum is being issued to clarify wording in Amendment #2, issued February 13, 2004.

The effective date for the requirement to offer the new version of the consent form included in Amendment #2 has been changed from March 15, 2004 to June 1, 2004. For participants currently on study or randomized prior to June 1, 2004, institutions must document that participants have been informed of this information via the "Dear Participant" letter. For participants randomized on or after June 1, 2004 the local consent form must contain the updated information provided in Amendment #2.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
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VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distributed: February 13, 2004
DCP Re-Submission: February 5, 2004

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

AMENDMENT #2

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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

AMENDMENT #2

Please note that the protocol referenced above has been amended to provide information regarding the results of two important and relevant studies.

Enclosed please find a "Dear Participant" letter outlining the results of the Prostate Cancer Prevention Trial (Thompson IM, Goodman PJ, Tangen C, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedos RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA, Jr. The influence of finasteride in the development of prostate cancer. NEJM 349:215-24, 2003.) and of an additional analysis of Nutritional Prevention of Cancer Trial (Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF, Jr., Park HK, Gross EG, Graham GF, Stratton MS, Marshall JR, Clark LC. Selenium supplementation and secondary prevention of non-melanoma skin cancer in a randomized trial. JNCI 95[19]:1477-81, 2003.). This letter has been created with valuable input from the SELECT Site Coordinators Committee and the SELECT National Participant Advisory Board.

This information is also reflected in the protocol with the addition of a parenthetical statement to the end of the fourth full paragraph on page 5, the addition of a sentence to the end of the fourth full paragraph on page 6, the addition of a sentence at the end of the first paragraph of Section 3.1b and the addition of two bibliography references (#75 and #76) on page 33.

The Model Informed Consent Form was amended accordingly to provide the information to newly randomized participants. The following sentence was added to the "Selenium" risks paragraph on page 40: "One study did report an increased risk of non-melanoma skin cancer (particularly squamous cell skin cancer) with selenium use in patients who had previously had this disease."

The following sentences were added into the "What Other Options Are There?" section on page 42: "One large study has shown that finasteride is effective in preventing prostate cancer in some men. However, men on the study who got prostate cancer while taking finasteride experienced a slightly higher rate of high grade tumors." The final sentence of this section was deleted.

For participants currently on study or randomized prior to March 15, 2004, institutions must document that patients have been informed of this information via the "Dear Participant" letter. For any participants randomized on or after to March 15, 2004 the local consent form must contain this information.

Dr. Lippman's e-mail address and the study Version Date have been updated on the face page.

Additionally, two new Tertiary Objectives have been added (Sections 1.8 and 1.9, page 4) to reflect the study leadership's interest in helping to assess the role of these agents in Alzheimer's disease, macular degeneration and cataract.

To clarify that the notation for "µg" and "mcg" are the same ("micrograms"), parenthetical clarifications have been added to the "Supplier" section of Section 3.1c (page 11) and the table in Section 7.4 (page 18).

Although the vitamin E dose is phrased in terms of IU (international units) on the Study Supplement bottles, it has been phrased in mg in the protocol. This formulation does have mg = IU equivalence at 400 mg = 400 IU. However, to avoid confusion, the references to "mg" (when referring to the formulation used in this protocol) in Sections 3.3b, 3.3c (page 12) and the table in Section 7.4 (page 18) have been changed to "IU".

The table and subsequent paragraphs in Section 3.6 have been amended to reflect the new multivitamin composition and source (page 14).

Section 7.7a.1 has been amended to allow a complex PSA (cPSA) of > 3.4 ng/ml as a prompt for biopsy recommendation.

Two sentences have been added to the second paragraph under "What are my Rights as a Participant" in the Model Informed Consent Form (page 44) to clarify that participants can remain part of the study and provide health information even if they have stopped taking supplements. Three sentences were deleted from the first paragraph of this section and the last sentence of the paragraph was edited. This was done to improve clarity.

Replacement pages are enclosed for the face page and pages 4 - 6a, 10 - 12, 14, 18, 19, 33, 40, 40a, 42 and 44. Please insert them into your copy of the protocol. Pages 6a and 40a were added to prevent extensive repagination. The "Dear Participant" letter is also enclosed.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
Perrigo - Mark Mincey
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

February 2004

Dear Participant:

First we want to thank you for taking part in SELECT! As you know, SELECT follow-up is scheduled to continue for several more years. During that time, we expect results of other research studies to be released. Here are the results of two recently published studies.

New Results on Selenium and Skin Cancer

Researchers published updated results on a study of skin cancer and selenium. The study showed that people on this study who took selenium (200 mcg) every day had a 17% higher rate of basal cell and squamous cell skin cancer than people who took a placebo. These cancers are not the more dangerous kind of skin cancer (melanoma). The 1,312 people in this study were at high risk for skin cancer because they had a lot of exposure to the sun. All of them had previously had one of these skin cancers. Therefore, we do not know whether these research findings would apply to 1) people without a prior history of skin cancer, 2) people without a lot of sun exposure and 3) African Americans who are at low risk for any skin cancers. In order to find any increase in risk for men on SELECT, we will be asking you questions about skin cancers as part of your routine visits.

Name of the Article: Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial.

Authors: Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, et al. Nutritional Prevention of Cancer Study Group.

Journal: Journal of the National Cancer Institute 95:1477-1481, 2003.

Finasteride and Prostate Cancer

On June 23, 2003, results from the Prostate Cancer Prevention Trial (PCPT) were released. This study was designed to see if the drug finasteride, also known as Proscar®, could prevent prostate cancer in men ages 55 and older. 18,882 men took either finasteride or placebo for 7 years. At the end of seven years, the participants were offered a prostate biopsy to see whether or not they had prostate cancer.

These data show that the men in the finasteride group were about 25% less likely to get prostate cancer than the men who were in the placebo group. Although men taking finasteride had fewer prostate cancers, they had a greater number of high grade prostate cancers. This type of cancer can spread quickly even if the tumor is small. In the entire group of men taking finasteride who were biopsied, 6% had high grade cancers while 5% of men on placebo had high grade cancers. Almost all the prostate cancers found during the study were found in an early stage, when they are very treatable. The reason men on finasteride had more high grade cancers is unknown. The researchers are still studying this. You may remain on SELECT whether or not you take finasteride. We will continue to ask you about your finasteride use at your routine visits.

Name of the Article: The influence of finasteride on the development of prostate cancer

Authors: Thompson IM, Goodman PJ, Tangen CM, Lucia MS, et al.

Journal: New England Journal of Medicine 349: 213-222, 2003.

Many thanks for your continued commitment to SELECT!

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

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distributed: October 8, 2003
DCP Submission: September 9, 2003

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

REVISION #2

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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

REVISION #2

Please note the following revisions to the protocol referenced above:

In Section 5.3 (page 15), the wording of allowable PSA for PCPT participants was changed to acknowledge the early closure of the study.

In Section 5.10 (page 16), participants in the NLST (National Lung Screening Trial) were added to the list of individuals participating in other clinical trials who are specifically not eligible to participate in SELECT.

Additionally, also in Section 5.10 (page 16) because of the final report of the PCPT study and the resulting changes in end-of-study procedures for PCPT participants, eligibility of men who participated in PCPT has also been refined: "Those individuals who were randomized to the PCPT prior to March 22, 1996 must have completed the PCPT end-of-study biopsy requirement during the end-of-study window (7 years ± 90 days) and the end-of-study biopsy results must have been returned and must not be positive for prostate cancer or high grade (Grade 2 - 3) PIN. Men randomized to PCPT on March 22, 1996 or after are not required to have completed the PCPT end-of-study biopsy requirement in order to be eligible for SELECT."

Replacement pages are enclosed for the face page, page 15 and page 16. Please insert them into your copy of the protocol and replace your electronic draft with the version dated 09/09/03.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
BioAdvantex Pharma, Inc. - David Aiello
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Quality Assurance
Cecil Runyons - PREADVISE
William Christen, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

Distributed: January 30, 2003
January 20, 2003

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

REVISION #1

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

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

REVISION #1

Please note the following revisions to the protocol referenced above:

1. The e-mail addresses and mailstop for the statisticians were updated on the face page and the version date was changed.

2. References to the approved country guidelines for the management of blood pressure in the United States and Canada have been added to Section 7.1 (page 17), 7.6a (page 18) and 9.0 (the Study Calendar - page 21). Additional clarification has been added in Sections 3.3b and 5.9 to provide background for blood pressure monitoring in the study, and reference #74 was added accordingly. The second part of Section 7.6a is now 7.6b and the remainder of the section has been renumbered accordingly. Page 19a was added to prevent extensive repagination.

3. A toxicity grading scale for dermatitis has been added as a new Section 8.4 (page 20a). The existing Section 8.4 was renumbered as Section 8.5. Page 20a was added to prevent extensive repagination.

4. A sentence was added in Section 11.3c (page 25) to clarify that additional analyses such as a main effects analysis and assessing the role of smoking and the effect of antioxidants on prostate cancer, will be performed.

5. In the guidelines for reporting adverse events in Section 16.0 (page 28) the reference to the SELECT Adverse Event Report was changed to Form 409, available under "As Needed Forms" on the SELECT Workbench.

6. OHRP has indicated that financial incentives such as free medication, lab studies or physical exams should not be listed as study benefits in the consent form. As a result, the final two paragraphs of the "Benefits" section of the Model Informed Consent Form have been deleted (page 42). Because this change is an administrative clarification, it will be at the discretion of each institution and the responsible Institutional Review Board (IRB) how to implement this change.

   Additionally, an editorial error has been corrected on this page - the word "added" was changed to "deleted" in the third paragraph of "What Other Options Are There?".

7. The participating Study Centers and Study Sites list in Appendix 19.5 has been updated to reflect current participating institution names and affiliations.

Replacement pages are enclosed for the face page and pages 12, 16 - 20, the new page 19a, the new page 20a, 21, 25, 28, 33, 42 and 61 - 69. Please insert the replacement pages into your copy of the protocol and replace your electronic draft with the version dated 1/20/03.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
BioAdvantex Pharma, Inc. - David Aiello
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

February 14, 2002

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

AMENDMENT #1

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

IRB Review Requirements

(√) Full board review required

( ) Expedited review allowed

( ) No review required

AMENDMENT #1

Please note the following amendments to the protocol referenced above:

1. The time frame for prestudy PSA and DRE has been changed from ≤ 180 days prior to randomization to ≤ 364 days prior to randomization. This is reflected in the Schema and in Sections 5.2, 5.3 and 9.0 of the protocol. Section 5.2 has also been clarified regarding DRE eligibility.

2. The second sentence of the "HRQL Sample" paragraph on page 9 of Section 2.0 was updated to reflect that the HRQL sample will be a sample of participants from all CCOP sites and selected VACSP sites. This update is also reflected in the Model Informed Consent Form (in the third paragraph under "Why is This Study Being Done?" and in the paragraph beneath the fourth bulleted item under "What is Involved in the Study?"), and in Appendix 19.4 (in the first subpoint under the section entitled "HRQL Sample" and in the paragraph under Table 2).

   In the third paragraph on page 10, the last sentence was corrected to indicate that details of the nutritional substudy to validate the food frequency questionnaire will be sent directly to a subset of SELECT institutions (not via the SELECT protocol).

3. The description of the selenium placebo has been updated in Section 3.2b. The placebo is composed of dicalcium phosphate only. This change is also reflected in the Model Informed Consent Form (in the third sentence under the "Placebo" paragraph under "What are the Risks of the Study?").

4. A typographical error has been corrected in the "Formulation" and "Supplier" information for vitamin E under Section 3.3c. The specific formulation of vitamin E in the study is *dl*-α-tocopheryl acetate.

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5. Section 5.4 has been clarified to indicate that for previous PCPT participants, the diagnosis of prostate cancer or high grade (Grade 2 - 3) PIN by either the Pathology Core Laboratory for PCPT OR by the local pathologist would render the potential participant ineligible.

6. Section 5.8 has been amended to clarify that the average daily dose limit for aspirin applies regardless of the reason for aspirin therapy, and to indicate that if a potential participant is also receiving Plavix®, his daily aspirin dose must be ≤ 81 mg. Participants must agree to inform their study physician if changes in the need for anticoagulation therapy occur during their participation in SELECT.

7. Section 5.9 has been amended to clarify that the blood pressure taken for eligibility purposes must be performed at the Randomization Visit. Additionally, a sentence was added to the "¥" footnote in the Study Calendar to help clarify the blood pressure requirements.

8. Section 5.10 has been amended to ask that participants must agree not to join another clinical trial involving a medical, surgical, nutritional or life-style intervention while participating in SELECT. Also, Section 5.10 has been clarified to indicate that participants in other clinical trials who are no longer receiving intervention and who are in the follow-up phase only may be eligible for SELECT, but that participants in the NCI's PLCO trial are not eligible for SELECT. Additionally, Section 5.10 has been clarified to state that for previous PCPT participants, the end-of-study biopsy results must have been returned and must not be positive for prostate cancer or high grade (Grade 2 - 3) PIN. A blank was added for recording the results of the end-of-study biopsies.

9. A new Section 5.11 has been added to state that individuals with retinitis pigmentosa are not eligible for SELECT. The remainder of Section 5.0 has been renumbered accordingly.

10. Section 7.1 has been amended to clarify that potential participants will be asked at the Initial Visit if they are willing to stop taking any individual vitamin E or selenium supplements or antioxidant mixes containing selenium or vitamin E if they are randomized. A reference to the Study Manual for clarification of allowable supplemented foods was also added here. Additionally, a comment was added to the first sentence of the second paragraph to indicate that the Initial Visit is considered Day 0.

    A note was added in the next-to-last paragraph to indicate the participants in a prior Southwest Oncology Group study (including **SWOG-9217**, PCPT) will keep their previously assigned participant ID number.

    Also, in the last paragraph of Section 7.1, a sentence was added to clarify that participants who are known to have a bloodborne infectious disease such as HIV or hepatitis will not have their blood specimens collected. This has also been clarified in the Model Informed Consent Form. A sentence was added to the "Submission of Materials" section of Appendix 19.3 to indicate that, for participants who are known to have a bloodborne infectious disease, only a Level 1 or Level 2 pathology submission is allowed.

11. In the Model Informed Consent Form the first sentence of the second paragraph under "What about Confidentiality?" has been revised to indicate that results from specimen research will not "routinely" be given to the participant or the investigator. Specific situations will be handled on a case-by-case basis.

Additionally, all of the options for participating in the optional substudies have been re-worded for clarity. A specific sentence giving permission for taking part in the contact database project was added just prior to the participant choice options at #2. Item #3 was clarified to indicate that the intent of this item is to solicit the participants' choice regarding participation in sub-studies requiring "ACTIVE participation" on the part of the participant.

The choices for participating in sub-studies on stored specimens were clarified and revised. Item #4A is a blanket refusal to participate in the collection of specimens. Item #4B is a blanket agreement to participate in ALL collection, storage and research associated with the collection of all three types of specimens requested in this study (blood, toenails and prostate tissue). Item #4C allows the participant to choose not only which types of specimens are to be collected, but also the type of research for which they may be used.

All randomized participants must be assessed to determine whether their choices reflect the explanations outlined above. If a participant's choices do not reflect his understanding of the explanations outlined above, he must be re-consented. If changes are made during the re-consent process that will impact Form 100, the institution must submit an updated Form 100 to the SELECT Statistical Center. The further need for re-consent of randomized participants is at the discretion of the local IRB. However, these options must be offered verbatim to future participants (unless specific wording changes have been requested from and approved by the Operations Office).

12. The participating Study Centers and Study Sites list in Appendix 19.5 has been updated to reflect current participating institution names and affiliations.

13. The SELECT Serious Adverse Event Report (Form 409) has been added to the SELECT Web Site. As a result, it no longer requires duplication in the protocol. Please remove this form from your copy of the protocol (formerly page 71) and access the form from the web site. This change is also reflected on page 50 with the deletion of Section 19.6.

Replacement pages are enclosed for the face page and pages 3, 9 - 12, 15 - 17, 21, 35, 38, 40, 42, 46, 47, 50, 52, 54, 57 and 61 - 69. Please insert the replacement pages into your copy of the protocol and replace your electronic draft with the version dated 2/14/02. Please remove the SELECT SAE Report Form from your copy of the protocol.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
BioAdvantex Pharma, Inc. - David Aiello
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

May 25, 2001

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

STATUS NOTICE

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@ccf.org

IRB Review Requirements

( ) Full board review required

(√) Expedited review allowed

( ) No review required

ACTIVATION REVISION

The study referenced above will be officially activated for participant recruitment effective July 25, 2001.

If you have not yet put the full protocol through your local IRB review process, please obtain full board review and approval prior to July 25th.

There are several other regulatory or logistical items which could prevent your institution from enjoying full participation in the study if we do not have documentation of these items in the data base by July 25th.

These items are listed below:

- IRB approval
- pharmacy information
- OHRP assurance
- 1572 and CV for participating investigators
- Human Research training certification for participating investigators

If you are not certain whether your institution has fulfilled all of these requirements, please contact the Membership Department at the Operations Office (210/677-8808).

Institutions are asked to refrain from conducting any formal media activity until Tuesday, July 24, when the National Cancer Institute will implement a nationwide media announcement. SELECT is a national study but it is a local story and the best news coverage will result from a unified day of events on the 24th. Interim recruitment guidelines and suggestions will be available on the SELECT workbench by mid-June.

We are working on obtaining translations of the Model Informed Consent Form and participant brochure in French and Spanish. We hope to be able to provide these to you prior to official activation.

Additionally, the following revisions have been made to the protocol document.

1. The activation date of 7/25/01 and the last updated date of 5/25/01 were added to the face page. Additionally, Dr. Klein's e-mail address was updated. The reference to NCIC (National Cancer Institute - Canada) was changed to CUOG (Canadian Urologic Oncology Group) after Dr. Klotz's name on page 2.

2. The second sentence of the "HRQL Sample" paragraph on page 9 of Section 2.0 was updated to reflect that the HRQL sample will be a sample of 18,000 participants from all CCOP sites and all VA sites. The last two paragraphs of Section 2.0 were updated to correctly reflect that nutrition substudy information will be routed through the participating Study Sites when it is available.

3. Section 3.2b was revised to correct an editorial error (the word "and" was deleted from the first sentence of the "Supplier" information). Section 3.6 was revised to update the final formulation and ingredients for the Study Multivitamin.

4. In Section 5.0:

    a. The first sentence of the section was moved to appear just prior to Section 5.1.

    b. PSA guidelines for previous PCPT participants were added into Section 5.3.

    c. Section 5.7 was revised to delete "and the specially formulated (optional) Study Multivitamin" from the first sentence.

    d. Section 5.8 was revised to indicate that the acceptable aspirin dose is an "average daily dose" ≤ 175 mg/day (to allow for alternate day dosing of 350 mg).

    e. A "NOTE" was added to Section 5.9 to indicate that participants may be receiving anti-hypertension medication at the time of randomization, to control their blood pressure.

f. Section 5.10 was revised to provide space for collection of PCPT Randomization Date and PCPT end-of-study biopsy Date (as applicable).

5. Section 7.1 was revised in the 3rd sentence of the first paragraph to indicate that any "equivalent" multivitamin must contain no vitamin E and selenium. The third bullet item under the second paragraph was clarified such that participants must not be "…taking or planning to take a multivitamin containing either selenium or vitamin E."

6. Section 7.6a was revised to provide a brief description of the annual limited Physical Exam.

7. Section 7.9 was clarified to indicate that participants will be removed from protocol treatment only when they have stopped taking **both** Study Supplements.

8. Section 8.2 was revised to provide reference to the CTC (NCI Common Toxicity Criteria) version 2.0 as the toxicity monitoring criteria for this study. Sections 16.0 and 19.1 were also revised to reflect the correct version number (2.0) for the CTC.

9. The Study Calendar (Section 9.0) was revised to delete the line for "Performance Status" and to add a blood pressure assessment at randomization.

10. Sections 9.0, 14.0, 15.3, 18.0, the first paragraph under "What are the Costs?" in the Model Informed Consent Form, and the "Specimen Consent Supplemental Sheets" were revised to correct editorial errors.

11. In the Model Informed Consent Form:

a. The following two sentences were added prior to the last paragraph under "Why is this Study Being Done?":

"While a formal study testing the effects of these supplements on preventing prostate cancer has not been done, the benefits of taking these supplements is strongly suggested. Please be aware that you have a twenty-five percent chance (1 in 4) of being assigned to receive neither of these supplements (placebos only)."

b. The second sentence of the second paragraph under "Optional Projects" was revised to add the words "..collected and …". The third paragraph in this section was deleted.

c. The first bullet item on page 38 was revised to indicate the administration of the questionnaire regarding diet and vitamin use at randomization.

d. The final paragraph on page 38 was revised to correct the description of the use of the check boxes at the end of the form.

e. The third bullet under #2 on page 39 was revised to clarify that the tissue samples will be prostate tissue samples obtained from a prostate surgery or biopsy (as outlined on the previous page).

f. The third paragraph under "What are the Costs?" was revised to indicate that the institution must indicate whether the prestudy PSA will be participant's financial responsibility or whether the institution intends to assist with this cost (prestudy PSA costs are not separately reimbursed by the study). The fifth paragraph under "What are the Costs?" was revised to include "office visits" and to clarify that the local institution is responsible for outlining the participant's financial responsibilities.

g. The information from the prior version of Form 100 was inserted into the text of the Model Informed Consent Form and was edited to indicate that the "tissue" mentioned in this form is "prostate tissue". Form 100 is now to be completed by the Study Site personnel rather than by the participant.

12. Section 19.4 and the Model Informed Consent Form were revised to indicate that all of the VA sites will be participating in the HRQL, and to indicate the relative accrual contribution anticipated from CCOP sites and VA sites to the HRQL sample.

13. The pagination for Appendix Sections 19.5 and 19.6 has been corrected. Additionally, Section 19.5 has been updated to provide a list of currently active Study Sites.

14. Finally, all references in the protocol to the "Veterans Administration" have been change to "Veterans Affairs" and all references to "VA sites" have been changed to "Veteran Affairs Cooperative Studies Program (VACSP) sites." These changes are reflected on pages 9, 11 -14, 35, 38, 54, 57 and 58.

Replacement pages are enclosed for the face page and pages 2, 9 - 18, 20, 21, 25 - 28, 34 - 36, 38, 39, 43, 46 - 48, 50, 54, 55, 57, 58 and 61 - 71. Form 100 should be removed from all copies of the protocol, as it will be maintained on the SELECT Workbench with the other data collection forms to be completed by Study Site personnel. Please insert the replacement pages into your copy of the protocol and replace your electronic draft with the version dated 5/25/01.

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

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
BioAdvantex Pharma, Inc. - David Aiello
VA Pharmacy Coordinating Center - Kathy Boardman, R.P.H.
Frederick Cancer Research and Development Center - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

November 6, 2000

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000**, "Selenium and Vitamin E Cancer Prevention Trial (SELECT)." Study Coordinators: Drs. E. Klein, S. Lippman, I. Thompson, W. Sakr, et al.

MEMORANDUM

Study Coordinator: Eric A. Klein, M.D. Phone number: 216/444-5591
E-mail: kleine@cesmtp.ccf.org

IRB Review Requirements

(√) Full board review required

( ) Expedited review allowed

( ) No review required

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. You will be informed as soon as this status changes.

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

cc: SELECT Statistical Center Staff - Evonne Lackey
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
BioAdvantex Pharma, Inc. - David Aiello
VA Pharmacy Coordinating Center - Kathy Boardman, R.P.H.
Frederick Cancer Research and Development Center - Demetrius Albanes, M.D.

SOUTHWEST ONCOLOGY GROUP

SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL (SELECT)

PHASE III

PARTICIPANTS: See Appendix Section 19.5

STUDY COORDINATORS:

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Selenium
Vitamin E

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SCHEMA

Initial Visit*

↓

Men ages ≥ 55 (African American men may be ≥ 50) with no prior history of prostate cancer

↓

Normal DRE, Total PSA ≤ 4 ng/ml
≤ 364 days prior to randomization

↓

Randomization
(≥ 28 days and ≤ 90 days after Initial Visit)

Placebo + Placebo	Selenium + Placebo	Placebo + Vitamin E	Selenium + Vitamin E

↓

Follow-up every 6 months for medical events, adherence and adverse events
Suggested annual DRE and suggested annual PSA
(Year 01 only: follow-up every 3 months; phone contact only at Months 3 and 9)

↓

Off Supplements

(originally planned for 7 to 12 years after randomization depending on
when the participant was randomized - all treatment for all participants was stopped 10/23/08)

1.0 OBJECTIVES

Primary Objective

1.1 To assess the effect of selenium and vitamin E alone and in combination on the clinical incidence of prostate cancer.

Secondary Objectives

1.2 To assess the effect of selenium and vitamin E alone and in combination on the incidence of other cancers including:

a. Lung cancer

b. Colorectal cancer

c. All cancers combined

1.3 To assess the effect of selenium and vitamin E alone and in combination on the following measures:

a. Prostate cancer free survival

b. Lung cancer free survival

c. Colorectal cancer free survival

d. Cancer free survival

e. Overall survival

f. Serious cardiovascular events

Tertiary Objectives

1.4 Quality of Life:

To assess the effect of selenium and vitamin E alone and in combination on Health Related Quality of Life (HRQL) as measured by the Physical and Mental Health Component Scales of the SF-36V.

1.5 Molecular Epidemiology:

a. To evaluate the association of biological molecular markers with the risk of prostate cancer, lung cancer and colon cancer.

b. To explore the relationship between the effects of study supplements on prostate cancer risk and genetic factors.

1.6 Pathology and Biomarkers:

To evaluate cellular and molecular markers from banked tissue on the biology of prostate carcinogenesis and study supplements effects.

1.7 Diet Supplement, Nutrient Intake and Plasma Nutrients:

a. To assess whether the effects of the study supplements on prostate cancer risk are conditional upon duration and dose of pre-randomization use of the study supplements.

b. To assess whether the effects of the study supplements are conditional upon intakes of other nutrients, foods and dietary supplements.

c. To assess the effect of other dietary nutrients and dietary patterns on prostate cancer risk.

1.8 To assess the effect of selenium and vitamin E in combination in the reduction of the incidence of Alzheimer's disease.

1.9 To test whether selenium or vitamin E reduces the risk of age-related macular degeneration or cataract.

1.10 To assess the effect of selenium or selenium plus vitamin E in the prevention of pulmonary function decrease as measured by FEV1.

2.0 BACKGROUND

Prostate cancer has been the most common malignant tumor (excluding non-melanoma skin cancer) in U.S. men for the last decade. It has been estimated that the lifetime risk of developing prostate cancer is 16.6% for Caucasian males and 18.1% for African-American males, and the overall prostate cancer mortality risk for men age 50 is 2.9%. *(1, 2)*

The dramatic increase in the number of cases of prostate cancer and the steady increase in mortality from prostate cancer which has only recently begun to decline has caused emphasis to be placed on improving early diagnosis so as to treat the disease at an earlier, potentially more curable stage. Although PSA-based screening regimens have resulted in a substantial stage migration and virtually eliminated tumors that are metastatic at the time of diagnosis, there is no direct evidence that screening results in improved mortality and the morbidity of various treatments remains substantial. *(3, 4)*

An ideal method to reduce the mortality and morbidity of carcinoma of the prostate would be through primary prevention: either through a reduction in the number of life-threatening, clinically-evident cases or through a reduced age-dependent rate of development of the disease, i.e., the disease would become evident 5, 10, or 15 years later than otherwise would occur. 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 preventive method difficult in practice. *(5)*

The recognition of the importance of the androgenic milieu of the prostate in the development of prostate cancer led to the Prostate Cancer Prevention Trial (**SWOG-9217**) with the drug finasteride. Finasteride is a testosterone analogue that competitively inhibits the enzyme type 2, 5-alpha reductase that converts testosterone to dihydrotestosterone (DHT) in the prostate and causes a profound reduction in circulating and cellular DHT. *(6)* Finasteride inhibits growth of prostate cancer cells in vitro and is an active preventive agent in certain prostate-carcinogenesis animal models. *(7, 8)* The PCPT (**SWOG-9217**) is an ongoing Phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy of finasteride in the prevention of carcinoma of the prostate. Accrual was initiated in October 1993 and ended in May 1997 with the successful randomization of 18,882 participants. Final analysis of PCPT is expected in 2004. (Please note that the PCPT was stopped early [in June 2003] because of a clear finding that finasteride reduced the incidence of prostate cancer. However, participants who did develop prostate cancer while taking finasteride experienced a slightly higher incidence of high-grade tumors. Researchers are continuing to analyze the data to find out the nature of the relationship between the finasteride and the high-grade tumors.) *(75)*

Study Rationale

In both selenium and vitamin E, the strongest evidence for their potential roles in preventing prostate cancer comes from secondary findings of two randomized, placebo-controlled clinical trials. The development of these two supplements has arrived at the stage where a randomized, placebo-controlled intervention is needed to test the primary hypothesis regarding these supplements' prostate cancer chemoprevention effects. *(9)* Data indicate that activities of selenium and vitamin E are complementary and that the two supplements act synergistically to inhibit carcinogenesis. *(10 - 14)* This evidence makes the 2 x 2 factorial design for simultaneously testing both supplements a particularly attractive option for the confirmatory Phase III trial. *(9)*

Preclinical and pharmacokinetic data: There are limited preclinical data on the effects of selenium or vitamin E on prostate cancer model systems. Selenomethionine has been demonstrated to inhibit the growth of the DU-145 cell line in a dose-dependent fashion in doses ranging from 45 - 130 µM, while normal fibroblasts required 1000-fold higher doses. *(15, 16)* In these experiments selenomethionine was shown to produce both aberrant mitoses and induce apoptosis. *(15)* Selenium has also been shown to inhibit cadmium-induced proliferation of human prostatic epithelium. *(17)* Alpha-tocopherol has been shown to synergistically inhibit both DU-145 and PC3 proliferation in combination with lycopene and to enhance the inhibitory effects of Adriamycin on DU-145 cells. *(18, 19)* In the in vivo setting, vitamin E inhibited dietary-fat promoted growth of LNCaP xenografts in an athymic mouse model. *(20)*

There are also very limited data on the pharmacokinetics of these supplements in humans. In the ATBC study, 50 mg alpha-tocopherol given PO daily was associated with a 4.9 mg/l greater increase in median serum levels compared to placebo at 3 years and remained higher than mean levels in the placebo arm for the length of the study. *(21, 22)* In the Clark trial, participants receiving 200 µg selenium per day increased serum selenium levels by 67% within 6 - 9 months of supplementation, while levels remained unchanged in the placebo group. *(34)* Swanson reported a kinetic model of selenium distribution and excretion in 6 healthy adults. *(23)* In this study a single oral dose of 200 µg l-selenomethionine revealed an average turnover time of .01 - 1.1 days in the plasma, 1.6 - 3.1 days in the liver-pancreas subsystem, and 61 - 86 days in peripheral tissues. The model also suggested substantial reutilization of labeled selenium. Duffield demonstrated that plasma and whole-blood levels of glutathione peroxidase activity and selenoprotein P increased with supplementation with 10 - 40 µg *L*-selenomethionine orally for 20 weeks in healthy individuals with low blood selenium levels, with a plateau observed only in those receiving the highest dose.

Vitamin E (Alpha-Tocopherol): Epidemiological studies have correlated vitamin E levels with prostate cancer mortality. Androgens may increase oxidative stress of cells. Oxidative stress increases with age and is directly related to a variety of cancer risks. *(24)* Vitamin E may be protective via its antioxidant activity or may have an independent inhibitory effect on prostate cancer cells. Vitamin E may decrease cancer risk through its effect on cellular structures (DNA and membrane), cell proteins, and immune function. A study of serum vitamin E levels in 2,974 subjects between 1971 and 1973, with a 17-year follow-up, found low levels of vitamin E were associated with higher prostate cancer risk. *(25)* Results of the recently completed Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study indicate a variety of intriguing leads for use of vitamin E in a healthy population. *(26)* The ATBC trial was a randomized trial conducted in more than 29,000 male smokers in Finland. Secondary findings regarding participants receiving vitamin E included a 40% decrease in Stage B or higher prostate cancer and a 32% decrease in all stages of prostate cancer. Overall during the 5-to-8-year intervention period, the number of new prostate cancer cases occurring in the vitamin E group (who received 50 mg daily) versus that in the non-vitamin E group was 99 versus 147, respectively.

The dose of vitamin E chosen for SELECT was based on several factors, including: (1) maximizing the opportunity for benefit for the primary endpoint, prostate cancer, as well as optimizing the potential for preventing secondary endpoints such as other cancer endpoints (e.g., lung and colorectal cancers) and (2) a well-established safety record for vitamin E from large randomized controlled trials such as HOPE (400 mg/d), Women's Health Study (600 mg qod), and CHAOS (Cambridge Heart Antioxidant Study). *(27, 28)* The formulation of vitamin E was kept consistent with the ATBC Study alpha-tocopherol preparation and includes a racemic mixture of all 8 isomers rather than targeting a single isomer (e.g., RRR alpha-tocopherol).

Selenium (Se): The other leading supplement with potential for chemoprevention of prostate cancer is selenium. The accumulated evidence supporting selenium is limited. *(10 - 13, 29 - 35)* Preliminary evidence comes from a nested case control study of selenium effects on advanced prostate cancer risk imbedded in a prospective design. This analysis included time-integrated assessment of status through selenium measurement in toenails, careful appraisal and control of other potential influencing factors and the largest number of advanced prostate cancer cases (N = 181) studied to date. Findings of this study suggest that the risk of advanced prostate cancer for men with the highest selenium status (estimated daily intake of 159 g/day) was one-half to two-thirds less than that in men with the lowest selenium status. *(33)*

A secondary analysis from a clinical trial is the primary evidence for selenium as chemoprevention of prostate cancer. This was a trial conducted by Clark et al. to prevent squamous or basal cell skin cancer with selenium in 1,312 patients with a history of non-melanoma skin cancer and a low-to-normal selenium status. *(34)* Subjects were randomly assigned to receive selenium (200 µg/day) or placebo. Follow-up time was an average of four and one-half years. The secondary-analysis results regarding prostate cancer showed a two-thirds reduction in incidence (13 vs. 35 prostate cancers in the selenium-treated group and placebo group, respectively). *(35)* In an additional analysis of this study, an increased risk of non-melanoma skin cancer (particularly squamous cell skin cancer) was seen. *(76)*

Selenomethionine was chosen as the preferred form of selenium for SELECT because it is the predominant form of selenium found in selenized yeast (yeast was used in both the Nutritional Prevention of Cancer Study and the General Population Trial in the Nutrition Intervention Trials in Linxian), it is well-characterized, highly bioavailable, and does not have the problem of batch-to-batch variability observed in the Nutritional Prevention of Cancer Study for yeast. *(34, 36)* The dose of selenium chosen (200 µg/d) is the same as was used in the Nutritional Prevention of Cancer Study, where efficacy was observed without toxicity.

Effects on PSA: No effect of vitamin E was seen on PSA levels in the ATBC study or in a sub-study conducted on banked serum from the HOPE trial. *(26)* No effect of selenium was seen on PSA in the Nutritional Prevention of Cancer Study or in a preliminary selenium/PSA analysis from the **S9812** limited institution pilot study in which men with prostate cancer are randomized to placebo or selenium for 2-4 weeks. *(J. Combs, Personal communication)* PSA measurements are at baseline and prior to prostatectomy.

Since there is no evidence that either supplement alone had an effect on PSA, we have no reason to believe that the combination of vitamin E and selenium will have an effect. The DSMC will look at Year 1 PSA values compared to baseline PSA values for each treatment arm to determine if further studies are necessary.

Study Components

Recruitment and Adherence

Because the sample size goal in SELECT is very large, the inclusion/exclusion criteria have been made as broad as possible. There will be an emphasis on randomization and over-representation of African-Americans because of the increased risk of prostate cancer in this minority group. Also, African-American men aged 50 - 55 have comparable prostate cancer incidence rates to Caucasian men aged 55 - 60. For this reason, this study will allow a lower age limit for eligibility for African-American men.

Minority Recruitment

The incidence of prostate cancer in African-Americans is higher than in other racial and ethnic groups (approximately 20% of all prostate cancers in the U.S. occur in African-Americans). Because of the proportion of the disease burden within African-Americans, SELECT will make every effort to have 20% of the randomized cohort be African-American. Despite considerable effort the final proportion of African-Americans in PCPT was less than 5%. Increased emphasis on recruitment from selected sites with a high proportion of African-Americans and experience from PCPT will be integral parts of the overall recruitment program. The Minority Recruitment Handbook, developed by the Southwest Oncology Group for the PCPT, will be incorporated into the SELECT Study Manual. In addition we propose to assemble a national advisory committee. These individuals will provide liaison and hopefully expand the entry of African-Americans through our recruitment efforts in order to help us meet our enrollment goals in SELECT.

Recruitment Strategies

Media strategies - National, regional, and local media outlets that serve minority audiences will be used to promote the trial. These may include syndicated radio, television programs, and print outlets as well as editorials and/or position papers in professional journals.

Educational strategies - Educational modules/programs will be developed in conjunction with the Cancer Clinical Trials Education Program (CCTEP) of the Office of Cancer Communications and the Leadership Initiatives (Black, Hispanic, and Appalachian). CCTEP partners (Association of Oncology Social Workers, the Cancer Information Service, and the Oncology Nursing Society) will be invited to participate in the planning and implementation of the recruitment effort.

Community lay health educators/recruiters - The National Black Leadership Initiative is comprised of a nationwide network of community-based coalitions. Coalitions from this Leadership Initiative will be selected to participate in an intensive training and recruitment intervention. These coalitions will be paired with local clinical sites for participation in the development, implementation and evaluation of a recruitment plan that is tailored to their locale.

Adherence

The overall adherence approach for this trial is based on two essential principles: 1) anticipation and prevention, and 2) implementation of an effective adherence plan beginning in the recruitment period. All investigators and clinical coordinators will be instructed as part of their preactivation Training Workshop and periodically will have refresher instruction in the overall adherence program.

Adherence Assessment

Adherence will be assessed by pill count every six months. Validation of pill count as a measure of adherence will be done in a sample of Study Sites by testing participants for serum levels of vitamin E and selenium. Approximately 6% of the participants will be in this sample.

Inclusion of Minorities and Underserved/Uninsured

It is a standing policy of the Southwest Oncology Group to include eligible patients and/or participants of both sexes and all races and ethnicities in all Group clinical trials, except as restricted by specific disease site (e.g., prostate, gynecological). The proposed participant population will consist of males, due to the specific disease site (prostate), and will include minority populations, including, but not limited to, African-Americans, Hispanics, Asian-Americans, as well as medically underserved populations. As African-American males are at higher risk for the development of prostate cancer, an attempt will be made to over-recruit this population through specific recruitment and adherence strategies. Previous minority accrual in Southwest Oncology Group genitourinary and cancer control studies in 1998 and other relevant studies is shown below:

ACCRUAL	**Total**	**White**	**Black**	**Hispanic**	**Other**
Committee (1998)					
GU	318	247 (77.7%)	57 (17.9%)	5 (1.6%)	9 (2.8%)
Cancer Control	532	447 (84.0%)	53 (10.0%)	13 (2.4%)	19 (3.6%)
PCPT (1994 - 1997)	18,882	17,272 (91.5%)	702 (3.7%)	497 (2.6%)	411 (2.2%)
Pivot Accrual (1994 - 1997)	578	379 (65.6%)	159 (27.5%)	27 (4.6%)	13 (2.2%)

Health Related Quality of Life

Quality of life is an important outcome measure to monitor in a trial with healthy participants who are asked to take a chemopreventive agent for a protracted period of time. Chemopreventive agents can have broad impacts on a participant's functioning as well as specific side effects associated with the agent. Health-related quality of life (HRQL) refers to a focus on areas of functioning that would be expected to be affected by a medical intervention, such as a chemoprevention; basic domains of functioning such as physical, emotional, role, and social functioning are of interest. *(37, 38)* An HRQL endpoint not only allows monitoring the effects of the chemopreventive agent on participant functioning but also communicates to participants that trial investigators are concerned enough about such effects to include their assessment as part of the trial design. A participant's expectations regarding the research team's concern for his well-being can affect willingness to enroll in a long-term trial. *(39)* The SF-36 Health Survey was designed to measure the health status of individuals in the general population and individuals who have various chronic diseases and health conditions. *(40 - 44)* It therefore is an appropriate measure for men volunteering to participate in a chemoprevention trial. In the PCPT, the SF-36 at enrollment was sensitive to age (< 63 vs. ≥ 63) and to the presence or absence of chronic health conditions such as diabetes, high blood pressure, and current smoking. *(45)*

The SF-36 Health Survey, Veterans version (SF-36V) will be used to measure HRQL in SELECT. *(46, 47)* Veterans Affairs (VA) researchers modified the SF-36 to increase the precision and discriminate validity for the role functioning scales and the two summary scales for assessment of patients in the VA ambulatory care setting. The main modification was to provide a five-level response format instead of a dichotomous (Yes/No) format for the two role functioning scales. *(46 - 48)*

Specifically, the Physical and Mental Component Scale summary scores of the SF-36V will provide the outcome variables for treatment comparisons in SELECT. Normative data are available for the SF-36 and will be available for the SF-36V by the time SELECT data are analyzed; SF-36V scores can be converted into SF-36 scores. *(49)*

We will also include a single-item measure of global HRQL, the UNISCALE, a visual analogue scale (VAS) measure with "lowest quality" and "highest quality" as the two anchor points. *(50, 51)*

The SF-36V and the UNISCALE will be administered at randomization, and at Years 1, 3, 5 and 7.

HRQL Sample:

Tests of equivalence for the five possible treatment arm HRQL comparisons are adequately powered with a subset of the full sample for SELECT. Therefore, we will select a subsample of participants from two major sources: all Community Clinical Oncology Program (CCOP) sites, and selected Veterans Affairs Cooperative Studies Program (VACSP) sites (listed on the SELECT web-based Workbench).

Dietary Assessment

The main purpose of nutrition-related measures in SELECT is to understand associations of the experimental supplements, vitamin E and selenium, with prostate cancer risk. Nutrition-related measures include behavioral and biological assessments of diet and nutritional supplement use and will be used to address the following aims:

1. To test whether the effects of study supplements on prostate cancer risk are conditional upon the following:
    a. duration and dose of pre-randomization use of supplemental vitamin E or selenium;
    b. pre-randomization concentrations of (a) serum vitamin E and selenium and (b) toenail selenium.
2. To test whether the effects of selenium and vitamin E supplementation on prostate cancer risk are conditional upon intakes of other nutrients, foods and dietary supplements that are putatively related to prostate cancer risk, including the following: fat (total, saturated, and specific fatty acids), carotenoids, soy, meat, and fruits and vegetables.

In addition to these aims, there are questions about the relationship of nutrient-related exposures with prostate cancer risk that can be addressed in this study. These include:

1. Is the use of other nutritional and dietary supplements, both pre- and post-randomization, related to prostate cancer risk?
2. Is the intake of other nutrients, in particular dietary fat, specific fatty acids, and carotenoids, related to prostate cancer risk?
3. Are dietary patterns, such as consumption of red meat, charred meats, soy products, and fruits and vegetables related to prostate cancer risk?

Results from these studies can be used to better understand the study's primary outcomes and will be important in formulating public health recommendations for prostate cancer prevention.

To achieve these aims, all participants will complete a food frequency questionnaire and a supplement use history questionnaire at baseline. Baseline blood and toenails also will be collected and stored for later analyses. At annual visits, all participants will complete a short questionnaire on supplements they used over the previous year.

In addition, a sample of 150 African-American and 150 white men will be recruited into a sub-study to validate the food frequency questionnaire. This study will be centrally administered by the staff of the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center. Details of this study will be forthcoming directly to a subset of SELECT institutions.

Men who agree to be contacted for future studies (on their informed consent) will receive letters through their Study Site from the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center inviting them into the validation study, and then will be contacted by phone. The men will complete separate informed consents for this substudy, which will include six telephone-administered 24-hour dietary recalls spread throughout the year, and a repeat food frequency questionnaire at the end of the sub-study. Men who participate will be compensated for their time.

Specimen Banking

Specimens have been collected and banked for future use in supporting study Objectives 1.5-1.7. Baseline bloods were collected for planned studies of the effects of genetic characteristics and baseline selenium and vitamin E status on prostate cancer risk and treatment efficacy. These bloods were processed centrally and frozen for later analyses. Approximately 8-10 ml of plasma, 3 aliquots of buffy coat (1 aliquot processed for lymphocyte immortalization), and 2 aliquots of red blood cells were stored from each participant. Recent experience from the Prostate Cancer Prevention Trial makes clear the value of post-randomization blood collections to support studies of prostate cancer etiology and risk. For example, post-randomization bloods will allow detailed studies of how oxidative stress, serum micronutrients and growth factors are affected by study treatments, and of how the temporal sequence of changes in these factors is associated with prostate cancer risk. Collection of these additional post-randomization bloods will provide additional strength to the study Objectives 1.5-1.7

3.0 SUPPLEMENT INFORMATION (IND-58,212)

Procedures for Study Supplement distribution are described in the SELECT Study Manual.

3.1 *L*-Selenomethionine (Selenium)

a. DESCRIPTION

Selenium (Se) is an essential nonmetallic trace element with an average nutritional intake of 50-350 μg/day and an estimated dietary MTD of 819 μg/day. Dietary selenium is predominantly in the form of organic compounds, primarily selenomethionine and selenocysteine, ingested in grains, meat, yeast, and some vegetables. Low Se status has been epidemiologically linked to increased incidence of cardiovascular disease and increased incidence or mortality from cancers in various organs, such as bladder, breast, colon and rectum, lung, and prostate.

b. TOXICOLOGY

Chronic selenium toxicity would be expected in humans after long-term consumption of more than 2,400 - 3,000 μg/day. Symptoms of toxicity include nausea, fatigue, irritability, dermatitis, cough, coryza, bronchitis, hair loss, halitosis, dizziness, nail tenderness, and lassitude. These symptoms are reversible. In one study, an increased risk of non-melanoma skin cancer (particularly squamous cell skin cancer) was seen with selenium use in patients who previously had this disease. *(76)*

Pregnancy and Lactation: Selenium has exhibited embryolethality and teratogenicity in birds and fish following exposure to inorganic or organic forms. Administration of *L*-selenomethionine to hamsters at doses of 75 and 100 μmol/kg/day over gestation days five through eight did not produce teratogenic effects. A single dose of 75 μmol/kg on gestational day eight significantly increased the incidence of abnormal litters, and also resulted in severe maternal toxicity. In macaque monkeys, doses of 25, 150, or 300 μg/kg/day during organogenesis (gestational days 20-50) did not increase the embryonic or fetal death rate compared to controls. No negative effects were found in the neonates, despite increased tissue Se levels. No human data are available.

c. PHARMACOLOGY

Kinetics: About 75% of an oral dose of *L*-selenomethionine is actively transported from the human intestine by the methionine carrier in humans. It may then be incorporated directly into proteins in place of l-methionine when levels of dietary methionine are low, catabolized to selenocysteine for incorporation into selenoproteins, or released into the Se pool by further catabolism or transsulfuration to trimethylselonium and be excreted in the urine. Organic Se compounds such as selenomethionine are sequestered and accumulate in tissues to a greater extent than inorganic forms of Se, especially in the kidney, liver, and muscle. A pharmacokinetic study of a single 200 μg dose to healthy males had a whole body-residence time approximately five times longer than the turnover time in the slowest tissue pool, suggesting considerable recycling of Se. The half-life is estimated to be 200 - 300 days.

Formulation: *L*-selenomethionine is available as capsules containing 25, 50, 100, 200, and 400 μg. The 200 μg capsule will be used for this study.

Administration: Oral

Supplier: Sabinsa, Inc. (Piscataway, NJ), has agreed to supply the *L*-selenomethionine, 200 μg (200 mcg) (elemental) capsules at cost for the duration of the trial. The costs for these supplements will be covered as part of the study grant from the National Cancer Institute. Packaging and distribution will be done through the Veterans Affairs Pharmacy Coordinating Center.

3.2 Selenium Placebo

a. DESCRIPTION

Formulation: Capsules identical in appearance to *L*-selenomethionine.

b. PHARMACOLOGY

Composition: Dicalcium phosphate.

Administration: Oral.

Supplier: Sabinsa, Inc. (Piscataway, NJ), has agreed to supply the *L*-selenomethionine matching placebo capsules at cost for the duration of the trial. The costs for these supplements will be covered as part of the study grant from the National Cancer Institute. Packaging and distribution will be done through the Veterans Affairs Pharmacy Coordinating Center.

3.3 Vitamin E (Alpha-Tocopherol)

a. DESCRIPTION

Vitamin E is a naturally occurring, essential, fat-soluble vitamin. Its importance in mammalian biology was revealed by the fertility research of Evans and Bishop. Vitamin E functions as the major lipid-soluble antioxidant in cell membranes; it is a chain-breaking, free-radical scavenger (including nitrogen reactive species), and inhibits lipid peroxidation specifically, activity relevant to carcinogen-induced DNA damage.

b. TOXICOLOGY

Few, if any, adverse effects are anticipated from the planned supplementation with vitamin E, 400 IU daily (a formulation having mg-IU equivalence). Decades of human research support the safety of this supplement, even at dosages 600, 800, and 1,200 IU/day, and the LD_{50} for vitamin E is in excess of 2,000 mg/kg for rats, mice, and rabbits. Four recently completed large controlled trials, representing over 60,000 participants, have involved chronic vitamin E (α-tocopherol) supplementation, at dosages of 30, 50, 400, and 800 IU/day. No significant adverse effects were reported with the exception of elevated risk of hemorrhagic stroke among male smokers in the ATBC Study, a finding that was subsequently isolated to the subgroup of men with systolic blood pressure $\geq$ 160 mm/Hg (the latter being an exclusion criterion in the present trial along with use of anticoagulant medication or history of hemorrhagic stroke). *(74)* (In the same trial, ischemic stroke and ischemic coronary events were reduced by the same vitamin E intervention.)

c. PHARMACOLOGY

At least 8 different tocopherols and tocotrienols have vitamin E biological activity. The most active form of vitamin E, α-tocopherol, is also the most widely distributed in nature and the predominant form in human tissues. For dietary purposes, vitamin E activity is expressed as vitamin E equivalents; i.e., biological effects equivalent to those from 1 mg of vitamin E. Vegetable oils and vegetable oil-containing products, such as margarine and shortening, are the richest vitamin E sources in the U.S. diet followed by whole-wheat products and nuts. The average vitamin E intake among men and women in the U.S. is estimated to be 10 mg/day and 7 mg/day, respectively. The recommended dietary allowance from the Food and Nutrition Board of the National Academies is set at 15 mg daily for men and women.

Formulation: The planned formulation vitamin E (*dl*-α-tocopheryl acetate) encompasses the 8 possible stereoisomers resulting methyl group positioning at the 2', 4', and 8' asymmetric carbon atoms. The 400 IU capsule will be used for this study.

Administration: Oral.

Supplier: Roche Vitamins, Inc. (Parsippany, NJ) will provide the vitamin E (*dl*-α-tocopheryl acetate) free of charge for the duration of the trial. Tishcon Corp. (Westbury, NY) has agreed to provide encapsulation free of charge for the duration of the trial. Packaging and distribution will be done through the Veterans Affairs Pharmacy Coordinating Center.

3.4 Vitamin E Placebo

a. DESCRIPTION

Formulation: Capsules identical in appearance to vitamin E. Theoretical composition of vitamin E placebo: Encapsulated soybean oil.

b. PHARMACOLOGY

Administration: Oral.

Supplier: Roche Vitamins, Inc. has agreed to provide a soybean oil placebo free of charge for the duration of the trial. Nutricia Manufacturing, USA, Inc. has agreed to provide encapsulation free of charge for the duration of the trial. Packaging and distribution will be done through the Veterans Affairs Pharmacy Coordinating Center.

3.5 Issues Regarding Combined Selenium and Vitamin E

The limited clinical data available on the combination of selenium and vitamin E do not indicate that there are additional toxicities associated specifically with the combination beyond what are described for the single supplements. The principal investigators of the Linxian, China, general population trial (with approximately 30,000 subjects) and ATBC Cancer Prevention Study (approximately 29,000 subjects) did not detect any toxicity associated with selenium and vitamin E interactions. *(21, 36, personal communication, Demetrius Albanes, National Cancer Institute)* The Linxian trial involved combined beta-carotene, selenium and vitamin E (at lower doses than those in SELECT), which produced no apparent toxicity. ATBC analyses of vitamin E interaction with selenium intake or supplement use have not shown increased adverse effects.

Investigators of the Clark et al. skin trial with selenium also report no known toxicity involving selenium interaction with vitamin E. *(34, personal communication, James R. Marshall, University of Arizona)* There were no excess adverse effects in either the 200 µg or 400 µg group of this trial. Although blood levels of vitamin E (which was not tested in this trial) were not recorded, any possibility that the subset of these patients who took vitamin E during the trial had complications is rendered extremely small by the limited overall adverse effect of selenium in the trial.

Experimental studies in animals support the idea that selenium and vitamin E work synergistically, but in a beneficial rather than adverse way, with greater protection from oxidative damage when they are given in combination rather than singly (particularly at the margins of deficiency for one or the other of the supplements). *(13, 14)*

3.6 In order to provide all SELECT participants with desirable multivitamin supplementation, but also to control levels of potentially confounding supplements and discourage participant "drop in", each participant and their significant other (if applicable) is provided with a specially formulated (optional) Study Multivitamin for the duration of their participation in the study.

The formulation includes

Nutrient	Amount	% Daily Value
Vitamin A* (20% as beta-carotene)	3,500 IU	70%
Vitamin C	60 mg	100%
Vitamin D	400 IU	100%
Vitamin K	10 mcg	13%
Thiamin	1.5 mg	100%
Riboflavin	1.7 mg	100%
Niacin	20 mg	100%
Vitamin B6	3 mg	150%
Folate	400 mcg	100%
Vitamin B12	25 mg	417%
Biotin	30 mcg	10%
Pantothenic Acid	10 mg	100%
Calcium	200 mg	20%
Phosphorus	48 mg	5%
Iodine	150 mg	100%
Magnesium	100 mg	25%
Zinc	15 mg	100%
Copper	2 mg	100%
Manganese	2 mg	100%
Chromium	150 mcg	125%
Molybdenum	75 mcg	100%
Chloride	72 mg	2%
Potassium	80 mg	2%
Boron	150 mcg	N/A
Nickel	5 mcg	N/A
Silicon	2 mg	N/A
Vanadium	10 mcg	N/A
INGREDIENTS: Calcium Carbonate, Dicalcium Phosphate, Magnesium Oxide, Potassium Chloride, Microcrystalline Cellulose, Ascorbic Acid, Acacia, Modified Cellulose Gum, Stearic Acid, Niacinamide, Zinc Oxide, Dextrin, Titanium Dioxide, Crospovidone, Calcium Pantothenate, Calcium Silicate, Hypromellose, Magnesium Stearate, Manganese Sulfate, Gelatin, Polyethylene Glycol, Silicon Dioxide, Pyridoxine Hydrochloride, Cupric Oxide, Riboflavin, Lecithin (Soya), Sodium Borate, Thiamin Mononitrate, Vitamin A Acetate, Chromium Chloride, Lactose*, Folic Acid, FD&C Blue #2 Lake, Beta-Carotene, Sodium Molybdate, Cholecalciferol, Potassium Iodide, FD&C Red #40 Lake, FD&C Yellow #6 Lake, Biotin, Cyanocobalamin, Nickel Sulfate, Sodium Metavanadate, Gluten, Phytonadione.		

*While lactose is included in this caplet, it is present in a minuscule amount (0.04% by weight). The FDA does not consider this amount of lactose large enough to be included on a label, but the current manufacturer has a policy of listing each and every ingredient in a product regardless of how tiny the amount might be.

The multivitamin is a once-a-day formulation in tablet form.

The multivitamin will be produced and provided free of charge for the duration of the trial. Distribution will be done through the Veterans Affairs Pharmacy Coordinating Center.

4.0 STAGING CRITERIA

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

5.0 ELIGIBILITY CRITERIA

SELECT Participant No. _____

Participant's Initials (L, F, M) _____

Considerations for Enrollment and Randomization

The following should be considered when evaluating a potential candidate:

Use your judgement to determine if the individual is physically and psychologically fit to participate in the study. This would include evaluating the participant's potential ability and willingness to come to regular study site visits and to swallow 2 capsules daily for 7 - 12 years.

The participant should be capable of reasonably normal activity. A participant who has a permanent disability that does not impair his ability to carry on all normal activities can be considered.

Individuals with other medical illnesses which, in the investigator's opinion, cannot be adequately controlled with appropriate therapy are ineligible.

Each of the criteria in the following section must be met in order for a participant to be considered eligible for randomization. This section may be used as a worksheet to confirm participant eligibility.

_____ 5.1 Participants must be male, age 55 or older. African American men must be age 50 or older.

Age _____

_____ 5.2 Participants must have a Digital Rectal Examination (DRE) deemed **NOT SUSPICIOUS FOR PROSTATE CANCER** in the judgment of the examiner. Participants with a suspicious DRE are ineligible even if a recent or subsequent biopsy is negative for cancer. The non-suspicious DRE must be performed ≤ 364 days prior to randomization.

Date of DRE _____

_____ 5.3 Participants must have a Total PSA ≤ 4.0 ng/ml ≤ 364 days prior to randomization.

Previous PCPT (**SWOG-9217**) participants:

- If the participant will be randomized ≤ 60 days after his final Total PSA test for PCPT (typically contact 80), the results of the PSA must be used in determining eligibility. A report of "Not Elevated" meets the PSA eligibility requirement. Do no further PSA testing for eligibility.
- If the participant will be randomized 61 - 364 days after his final Total PSA test for PCPT, the investigator may choose to use either the results of that PSA (with a report "Not Elevated") or a new Total PSA test ≤ 364 days prior to randomization with the results of ≤ 4.0 ng/ml for eligibility.
- If the participant will be randomized > 364 days after his final PSA test for PCPT, a new Total PSA test ≤ 364 days prior to randomization with the result of ≤ 4.0 ng/ml is required.

Date of PSA _____ Total PSA value _____

_____ 5.4 Individuals previously diagnosed with prostate cancer or high grade (Grade 2 - 3) Prostatic Intraepithelial Neoplasia (PIN) are ineligible. (For previous PCPT participants, the diagnosis of prostate cancer or high grade [Grade 2 - 3] PIN by either the Pathology Core Laboratory OR by the local pathologist would render the potential participant ineligible).

SELECT Participant No. _____

Participant's Initials (L, F, M) _____

——— 5.5 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 randomization.

——— 5.6 Participants must be randomized ≥ 28 and ≤ 90 days after the Initial Visit (Initial Visit is considered Day 0).

Date of Initial Visit _____

——— 5.7 Participants must not be currently taking (on day of randomization) or planning to take the following in addition to Study Supplements:

- Any vitamin E
  or
- Any selenium

——— 5.8 Individuals currently receiving anticoagulation therapy (e.g., warfarin) are ineligible. Individuals taking aspirin for coagulation prophylaxis or for any other reason, must not exceed an average daily dose of 175 mg/day. If potential participants are also receiving Plavix®, their daily aspirin dose must not exceed 81 mg. Participants must agree to inform their study physician if changes in the need for anticoagulation therapy occur during their participation in SELECT.

——— 5.9 Participants must not have a history of hemorrhagic stroke. Participants must have a systolic blood pressure of < 160 mm/Hg and a diastolic blood pressure < 90 mm/Hg at the Randomization Visit. NOTE: Participants may be receiving anti-hypertension medication at the time of randomization. These blood pressure criteria were chosen based on an elevated risk of hemorrhagic stroke among male smokers in the ATBC study with systolic blood pressure ≥ 160 mm/Hg. Men with elevated blood pressure who have systolic < 160 mm/Hg AND diastolic blood pressure < 90 mm/Hg have not shown to be at increased risk of hemorrhagic stroke. See Section 7.1 for the management of participants with a systolic blood pressure ≥ 140 mm/Hg or a diastolic blood pressure ≥ 90 mm/Hg.

BP _____

——— 5.10 Individuals who are participating in any other clinical trial involving a medical, surgical, nutritional, or life-style intervention are ineligible (unless they are no longer receiving the intervention and are in the follow-up phase only). Participants must also agree not to join such a trial while participating in SELECT. Participants in the PLCO (Prostate, Lung, Colorectal and Ovarian screening trial) or the NLST (National Lung Screening Trial) sponsored by the National Cancer Institute are specifically not eligible to participate in SELECT.

Those individuals who were randomized to the PCPT prior to March 22, 1996 must have completed the PCPT end-of-study biopsy requirement during the end-of-study window (7 years ± 90 days) and the end-of-study biopsy results must have been returned and must not be positive for prostate cancer or high grade (Grade 2 - 3) PIN. Men randomized to PCPT on March 22, 1996 or after are not required to have completed the PCPT end-of-study biopsy in order to be eligible for SELECT.

Date of PCPT end-of-study biopsy _____ End-of-study biopsy result _____

Date of PCPT randomization _____

——— 5.11 Individuals with retinitis pigmentosa are not eligible.

——— 5.12 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.

——— 5.13 At the time of randomization, the Study Site name and ID number must be provided to the Statistical Center during the randomization program in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the database.

6.0 RANDOMIZATION SCHEME

6.1 Randomizations will be balanced by permuted block within each Study Site.

6.2 A web-based randomization system at the Southwest Oncology Group Statistical Center will be used to randomize participants.

7.0 TREATMENT PLAN

For treatment or toxicity related questions please contact Dr. Eric Klein at 216/444-5591 or Dr. Scott Lippman at 713/745-3672.

The policies, procedures and forms required to implement the SELECT Treatment Plan are included in the SELECT Study Manual and SELECT Workbench.

7.1 At the Initial Visit, potential participants will review and may sign the consent form. They will be asked if they are willing to stop taking any individual vitamin E or selenium supplements or antioxidant mixes containing selenium or vitamin E if they are randomized. Potential participants may continue to take a multivitamin and should be informed that if they are interested in being randomized to the study that they must be willing to substitute the specially formulated (optional) Study Multivitamin for the one they are currently taking, or an equivalent multivitamin (containing no vitamin E and selenium), or no multivitamin. Please see the Study Manual for clarification of allowable supplemented foods.

Randomization must take place between 28 and 90 days after the Initial Visit (the Initial Visit is Day 0). Potential participants will return to the Study Site and will be asked to bring in the dietary supplements that they are taking. This is to make sure that:

- they are not taking or planning to take any individual supplements of selenium or vitamin E
- they are not taking or planning to take antioxidant mix containing selenium or vitamin E, or
- they are not taking or planning to take a multivitamin containing either selenium or vitamin E.

At the Randomization Visit, the participant's blood pressure must be taken. **In the interest of general health, a participant with a systolic blood pressure $\geq$ 140 mm/Hg or a diastolic blood pressure $\geq$ 90 mm/Hg at randomization should have his blood pressure rechecked during that visit. If upon recheck the systolic blood pressure is $\geq$ 140 mm/Hg or the diastolic blood pressure is $\geq$ 90 mm/Hg, the participant should be referred to his primary care source for further evaluation and/or treatment.**

Primary care physicians should be urged to treat SELECT participants' blood pressure (both systolic and diastolic) according to the guidelines published respectively by the USA* and Canada.**

***The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.**

****2001 Canadian Recommendations for the Management of Hypertension: Part One - Assessment for Diagnosis, Cardiovascular Risk, Causes and Lifestyle Modification. Can J Cardiology 2002; 18(6): 604-624.**

Participants who meet eligibility criteria as defined in Section 5.0 and who have signed the Informed Consent will be randomized.

The randomization program will assign a unique participant ID number and the Study Supplement ID numbers for the initial bottles of Study Supplements. Participants in a prior Southwest Oncology Group study (including **SWOG-9217**, PCPT) will keep their previously assigned participant ID number. A six-month supply of Study Supplements will be dispensed. A specially formulated (optional) Study Multivitamin will also be available for dispensing at six-month intervals for randomized participants and their significant other.

With the participant's consent, blood and toenail specimens will be collected and submitted as described in the SELECT Study Manual and in Section 15.0. Participants who are known to have a bloodborne infectious disease (such as HIV or hepatitis) will not have the blood specimen collected.

7.2 Potential participants who initially fail to meet eligibility criteria may be reassessed for eligibility. All eligibility criteria must be met during subsequent assessments in order for the potential participant to be randomized. It is recommended that potential participants' eligibility for randomization be reassessed no more than twice.

7.3 The participant must begin Study Supplements within seven days following randomization.

7.4 Treatment Schedule (all treatment ended 10/23/08)*

SUPPLEMENT	DOSE	ROUTE	FREQUENCY	DURATION OF TRIAL
Selenium matched placebo	1 capsule	po	qd	7 years minimum, 12 years maximum*
Vitamin E matched placebo	1 capsule	po	qd	
Selenium	200 µg (200 mcg) (1 capsule)	po	qd	7 years minimum, 12 years maximum*
Vitamin E matched placebo	1 capsule	po	qd	
Selenium matched placebo	1 capsule	po	qd	7 years minimum, 12 years maximum*
Vitamin E	400 IU (1 capsule)	po	qd	
Selenium	200 µg (200 mcg) (1 capsule)	po	qd	7 years minimum, 12 years maximum*
Vitamin E	400 IU (1 capsule)	po	qd	

The specially formulated (optional) Study Multivitamin may be taken in addition to the Study Supplements on each arm of the study. The multivitamin may be started or stopped at any point during the study. (The study multivitamin supply will be discontinued prior to initiation of centralized follow-up to begin in November 2009.)

	DOSE	ROUTE	FREQUENCY	DURATION OF TRIAL
(Optional) Specially Formulated Study Multivitamin	1 tablet	po	qd	7 years minimum, 12 years maximum

7.5 Participants will be contacted for follow-up by telephone at three months and nine months during the first year after randomization. Participants will return to the Study Site every six months during all years. At each contact, study forms will be completed; participants will be assessed for adherence and adverse effects every six months through their next six month visit following the end of Study Supplements, and the next six-month supply of the specially formulated (optional) Study Multivitamin will be dispensed. Beginning November 2009 participants will be transitioned to centralized follow-up (see Section 7.13 below).

7.6 Annual Visit

a. On an annual basis (based on randomization date) the participant will have a limited Physical Exam including blood pressure, weight measure and smoking status update. **In the interest of general health, a participant with a systolic blood pressure ≥ 140 mm/Hg or a diastolic blood pressure ≥ 90 mm/Hg during the trial should have his blood pressure rechecked during that visit. If upon recheck the systolic blood pressure is ≥ 140 mm/Hg or the diastolic blood pressure is ≥ 90 mm/Hg, the participant should be referred to his primary care source for further evaluation and/or treatment.**

Primary care physicians should be urged to treat SELECT participants' blood pressure (both systolic and diastolic) according to the guidelines published respectively by the USA* and Canada.**

***The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.**

****2001 Canadian Recommendations for the Management of Hypertension: Part One - Assessment for Diagnosis, Cardiovascular Risk, Causes and Lifestyle Modification. Can J Cardiology 2002; 18(6): 604-624.**

b. It is suggested that participants have a digital rectal exam (DRE) and PSA determination completed in accordance with the standard of care at the Study Site and participant preference. Exams should be performed ≤ 42 days before or after the annual visit date and may be completed by either the Study Site staff or the participant's primary care physician. (See the SELECT Study Manual for additional information).

c. For Study Sites selected to participate in the serum vitamin E and selenium levels for adherence assessment, blood should be drawn (see Section 15.2 of this protocol and the SELECT Study Manual for details). Collection of specimens for the adherence assessment substudy ended in June 2009.

d. Participants who are removed from treatment for any reason other than prostate cancer or death should continue to have their annual visit performed as outlined in 7.6a. Requirements for endpoint reporting, management of an abnormal DRE and/or PSA will be the same as those for participants followed on supplements.

e. Participants are requested to consent to submission of an additional blood sample for banking at their 5 year annual visit or at their next visit after 10/23/08 (see the SELECT Study Manual for procedures).

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

a. DRE and PSA results for which biopsy is recommended include:

1. Total PSA by monoclonal antibody assay > 4.0 ng/ml or a complex PSA (cPSA) > 3.4 ng/ml.

2. A rise in annual total PSA of > 0.75 ng/ml within the last year.

3. Abnormal DRE.

4. Any clinical situation deemed appropriate.

The study **recommends** that the participant and physician consider the transrectal ultrasound (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.

If the participant chooses to undergo TRUS and biopsy, TRUS and biopsy should be performed within 28 days after the recommendation.

For details about these guidelines consult the American Urologic Association (AUA) Best Practice Guidelines.

b. After the participant has been biopsied, his management will be based on the pathologic results.

1. Benign and Grade 1 Prostatic Intraepithelial Neoplasia (PIN): The participant remains on treatment.

2. High Grade (Grade 2 - 3) Prostatic Intraepithelial Neoplasia (PIN): The participant should be rebiopsied within two months of the prior biopsy. If the repeat biopsy is benign or reveals PIN (Grade 1-3) the participant will remain on protocol treatment.

3. Prostate cancer: The participant should be removed from protocol treatment per Section 7.9. Upon the diagnosis of prostate cancer, staging will be accomplished in accordance with standard clinical practice (see Appendix 19.2).

c. Transrectal ultrasound (TRUS) should be performed by a clinician experienced in this procedure. Biopsies may be performed following standards set by each individual study site. Suggested techniques are listed below.

1. Sextant biopsy: A minimum of 6 biopsies of the peripheral zone should be performed 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. *(72)* In addition, any palpably abnormal areas and/or hypoechoic lesions seen on TRUS should be biopsied. The needle path should be directed so as to maximize the sampling of the peripheral zone of the prostate.

2. An alternative to the sextant biopsy technique is the 5-region technique recently described by Eskew et al., along with biopsies of palpable abnormalities and hypoechoic lesions. *(73)* In glands of greater than 40 cc in volume, more than 6 biopsies should be obtained based on published observations that the sextant technique undersamples larger glands. Transition zone biopsies may be included at the discretion of the investigator, but are recommended only in those patients with an abnormal PSA and a previously negative biopsy.

7.8 Participants found to have prostate cancer, suspicious findings or high grade (Grade 2 - 3) Prostatic Intraepithelial Neoplasia (PIN) at the time of biopsy, will have specimens submitted to the SELECT Pathology Review Laboratory for centralized review in accordance with Section 12.0 and Appendix 19.3.

7.9 Criteria for Removal from Protocol Treatment:

The reason for removal from treatment must be documented on study forms as described in the SELECT Study Manual.

Participants will be removed from treatment only when they have stopped taking **both** study supplements. Participants will be removed from protocol treatment under the following circumstances:

a. Diagnosis of prostate cancer.

b. Termination of protocol treatment (7 to 12 years after randomization depending on when the participant was randomized). All protocol treatment was ended on 10/23/08.

c. Diagnosis of an intercurrent illness that would, in the judgment of the treating physician, affect assessments of clinical status to a significant degree and/or require discontinuation of supplements. Participants should continue the Study Supplements if other medical events occur which are not considered to be supplement-related (e.g., cardiovascular event, diabetes). This determination will be made by the treating physician.

d. Unacceptable adverse effects.

e. Missed contacts. The participant missed receiving all study supplements for more than 1 year or missed more than two consecutive Study Site Visits.

f. Personal decision. The participant may withdraw from the study at any time for any reason.

7.10 Participants who are removed from treatment for any reason other than prostate cancer or death will require a health status update at six months and annual follow-up as described in Section 7.6. Participants with a diagnosis of prostate cancer will be followed annually for a vital status, prostate cancer treatment and study endpoints update.

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

7.12 Participant's treatment will be unblinded upon request. Instructions for unblinding participants are included in the SELECT Study Manual. Participants will be notified of the Study Supplements to which they were randomized at the time of the participant's Transition Visit (planned to occur between 11/2009 and 12/2010).

7.13 Transition to Centralized Follow-Up (see also Appendix 19.8)

It is expected that the transition process to centralized follow-up will be completed by the end of the calendar year 2010. During this time, each participant will have a Transition Visit at his local SELECT Study Center/Site. At this visit, participants will be asked to allow the transition of their follow-up to the centralized SELECT Coordinating Center. The process for transitioning to centralized follow-up will require local IRB review and approval at the participating Study Centers/Sites and will also require that the participant complete a new informed consent and agree to provide the SELECT Coordinating Center with detailed personal contact information.

Transition Visit

All participants will be asked to provide the routine follow-up data. For participants who have reported a diagnosis of prostate cancer and for whom a specimen is not stored at the biorepository, the site staff will request a medical release to be forwarded to the SELECT Pathology Review Laboratory for follow-up.

A new blood sample will be requested from participants who have reported a diagnosis of prostate cancer.

Prior to the participant's transition visit, site staff will contact the participant to inform him of the opportunity of continued follow-up through the SELECT Coordinating Center. A fact sheet describing the nature of the future follow-up, informed consent documents and appropriate data collection forms will be sent to the participant. At the time of the transition visit, staff will answer the participant's questions about the centralized follow-up, obtain consent and detailed participant contact information, and provide unblinding if the participant had not yet been unblinded and informed of his Study Supplement assignment. The CRA will send a copy of the signature page of the consent form to the SELECT Coordinating Center and will enter the contact information into the SELECT data base via the web; these actions will trigger the SELECT Coordinating Center's first direct contact with the participant. A participant who declines to consent for centralized follow-up will have completed his participation in SELECT and will not be approached further.

Centralized Follow-up

The SELECT Coordinating Center will mail data collection forms to each participant in the month of the participant's birth. Data collection may address any of the objectives stated in Section 1.0 of the **S0000** protocol. Participants will have the option to return completed forms by mail or to enter their data via a secure web application. Participants who do not respond to the mailing will be sent follow-up mailings; SELECT Coordinating Center staff will telephone non-responders to collect the data by phone.

For participants who report endpoints, SELECT Coordinating Center staff will request medical releases as appropriate. For prostate cancers, participants will be asked to sign a medical release for pathology reports and tissue; SELECT Coordinating Center staff will forward these medical releases to the SELECT Pathology Review Laboratory. For other primary cancers, participants will be asked to sign a medical release for pathology reports. SELECT Coordinating Center staff will obtain these reports and confirm the cancer diagnosis.

The SELECT follow-up forms will continue to collect information related to the SEE and ACP substudies. For participants who report an eligible event for SEE or ACP, the SELECT Coordinating Center will request medical releases and forward the releases to the appropriate ancillary study office. That office will then request the appropriate records and specimens (if applicable) from the participant's physician.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 For treatment or toxicity related questions please contact Dr. Eric Klein at 216/444-5591 or Dr. Scott Lippman at 713/745-5439.

8.2 There will be no modifications to the study supplement dose. Toxicities will be monitored using the CTC (NCI Common Toxicity Criteria) version 2.0 (see Section 19.1).

8.3 For assessment of halitosis for routine toxicity reporting, use the following criteria:

Halitosis (bad breath)

Grade 1	Mildly altered from baseline
Grade 2	Moderately altered from baseline

8.4 If dermatitis (as opposed to the symptoms of rash, pruritis, etc.) is diagnosed in a participant, the following grading scale should be used:

Dermatitis

Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Moist desquamation other than skin folds and creases; may include bleeding induced by minor trauma or abrasion
Grade 4	Skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding

8.5 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

		Randomization	Post-Randomization			Off Supplements		
REQUIRED STUDIES	**Initial Visit**	**Randomization Visit**	**3 and 9 month phone calls†**	**6 month visits**	**Annual visits**	**Annual visits**	**Transition Visit**	**Annual Centralized Follow-Up**
Participant Demographics		X						
Contact Information	X	X	X†	X	X	X	X	X
Medical History		X						
Unblind Participant							X	
Obtain consent for centralized follow-up							X	
PARTICIPANT REPORT								
Participant Lifestyle and Characteristics		X						
Health Survey SF-36V		X√			X√	X√		
Dietary Supplement and Food Questionnaire		X						
Current Dietary Supplement Use					X	X	Xα	
Family History		X						
Medical Events								X
STAFF REPORT								
Medical Events				X	X	X	X	
Supplement Adherence and Resupply				X	X			
Side Effects Assessment				X	X			
Annual Physical Exam					X	X	Xα	
CLINICAL								
Blood Pressure	X¥	X¥			X¥		X¥α	
DRE		X*			Suggested	Suggested	X*α	
Prostate Biopsy/TRUS					X#*f*	X#*f*	X#*f*	
LABORATORY								
PSA		X*			Suggested	Suggested	Suggested α	
Blood sample for banking		X			Xβ		Xy	
Toenail sample for banking		X						
Blood Sample for Adherence		X¢		X¢	X¢	X¢		
ENDPOINT ASSESSMENT								
Prostate Cancer £				X*f*	X*f*	X*f*	X*f*	X*f*
Other Primary Cancer £				X	X	X	X	X
Cardiovascular event £				X	X	X		
Death £				X	X	X	X	X
DRUG DISTRIBUTION								
Blinded Study Supplements Ω		X						
Study Multivitamin (optional) Ω		X		X	X			

NOTE: All forms to be utilized for SELECT will be available via the SELECT web site. Forms completion and submission guidelines are found in the SELECT Study Manual.

† During the first year only. Submit required form(s). These calls may be conducted per Study Site discretion in subsequent years, but no forms submission is required for these contacts.

√ HRQL data will be collected on a subset of participants at designated Study Sites - prior to randomization and at years one, three, five and seven after randomization (see Appendix 19.4 and the SELECT Study Manual).

¥ Per Section 5.9, the participant must have a systolic blood pressure of < 160 mm/Hg and a diastolic blood pressure of < 90 mm/Hg at the Randomization Visit to be considered eligible for the study. However, any participant with a systolic blood pressure ≥ 140 mm/Hg or a diastolic blood pressure ≥ 90 mm/Hg at randomization or subsequent clinic visits during the trial should have his blood pressure rechecked during that visit. If upon recheck the systolic or diastolic blood pressure is in excess of a systolic blood pressure ≥ 140 mm/Hg or a diastolic blood pressure ≥ 90 mm/Hg, the participant should be referred to his primary care source for further evaluation and or treatment. Primary care physicians should be urged to treat SELECT participants' blood pressure (both systolic and diastolic) according to the guidelines published respectively by the USA* and Canada.**
*The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
** 2001 Canadian Recommendations for the Management of Hypertension: Part One - Assessment for Diagnosis, Cardiovascular Risk, Causes and Lifestyle Modification. Can J Cardiology 2002; 18(6): 604-624.

Performed only on participants whose PSA or DRE indicate.

β Participants are requested to consent to submission of an additional blood sample for banking at their 5 year annual visit or at their next visit after 10/23/08.

f Pathology submission is also required if a procedure yields tissue deemed suspicious for prostate cancer or high grade (Grade 2 - 3) PIN (see Sections 7.8, 12.0 and 19.3).

£ Supporting documentation for endpoints should be collected and maintained in the participant's chart, and submitted to the Statistical Center upon request.

¢ Collected on a subset of participants at designated Study Sites at randomization, 6 months, 1, 2, 4, 6, 8 and 10 years after randomization.

Ω See Section 7.4 for study supplement schedule

* DRE and PSA value required ≤ 364 days prior to randomization per Sections 5.2 and 5.3. Annual DRE/PSA is suggested but not required.

α If the Transition Visit is also an Annual Visit.

y Only for participants with a diagnosis of prostate cancer.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 The primary endpoint of this study is prostate cancer incidence as determined by routine clinical management and confirmed by central pathology review. Prostate cancer diagnosis is determined by either:

a. Histologic evidence of prostate cancer on biopsy of prostate, lymph node, or other organ.

b. Total PSA > 50 ng/ml and positive bone scan.

10.2 Prostate cancer-free survival is defined as the period of time between randomization and death or diagnosis of prostate cancer.

10.3 Other cancers will be determined based on pathological, clinical and/or imaging evidence.

Lung cancer-free survival and colon cancer-free survival are defined as the period of time between randomization and death or diagnosis of lung cancer or colon cancer, whichever is applicable. Overall cancer-free survival is defined as the period of time between randomization and death or diagnosis of any cancer, including prostate cancer.

10.4 Cardiovascular events will be grouped using the Cardiovascular Health Study classification system and definitions for various event categories, and the NCI Common Toxicity Criteria. A serious event is defined as a Grade 3 - 5 event.

11.0 STATISTICAL CONSIDERATIONS

The primary endpoint will be prostate cancer incidence, as determined by routine clinical management.

Under the null hypothesis, there will be no difference in prostate cancer incidence between the specified intervention and placebo (Relative Risk = 1.0). The alternative hypothesis is that the incidence of prostate cancer will be reduced by 25% or more for a single supplement vs. placebo or for the combination vs. an effective single supplement (Relative Risk $\leq$ 0.75).

Under the assumptions outlined in Section 11.1 the effective relative risk of 0.75 is translated to a relative risk of 0.58 under conditions of perfect compliance. The underlying assumptions used to derive the sample size and power are based on the following: study duration, prostate cancer incidence, medication rate, drop-in rate, and competing risks. The design assumptions are based on PCPT, the ATBC and other related trials.

11.1 Design Assumptions

a. Study Duration

Study duration will be twelve years, with a five-year uniform accrual period and a minimum of seven years of treatment. Participants will receive study medication until a common point in time (the entire length of the trial is between seven and twelve years depending on when the participant was randomized).

b. Incidence Rate

The baseline incidence rate for prostate cancer for men on placebo for years 0 – 3 is given by PCPT rates. Prostate cancer incidence rates for the following years are estimated from the SEER 1991-1995 rates for all races combined. Based on PCPT, expectations are that participants will average 63 years of age at study entry. For each follow-up year 4 - 12 the estimate is calculated by the rate for a man aged 63 + s (where s = subject time in years since randomization).

The yearly prostate cancer incidence figures (PCPT/SEER rates) used in the sample-size calculations begin at 0% at randomization, .14% at year one and rise steadily to 1.36% twelve years later.

c. Medication Rate

Medication rate is an estimate of the adherence of participants on active study supplement. It is quantified by the percent of full active supplement dose taken by men in the specified arm. It is assumed that the medication rate will vary over time. We assume that medication rates for active supplements will decline from 100% at randomization to 51% at the end of twelve years of treatment. These estimates are based on off treatment rates for PCPT for the first 4 years of the study extrapolating the rate in the 4^{th} year to year 12.

d. Drop-in

Drop-in is defined as participants on placebo who are, in addition, taking active medication. It is assumed to be a constant 10% for the twelve years of treatment.

e. Competing Risks – Death and Loss

The cumulative competing risk is defined to be the estimated cumulative all-cause mortality rate plus the cumulative Lost-to-Follow-Up (LTFU) rate. The mortality rates used are from PCPT for the first four years and then adjusted upwards to the 1995 U.S. rates for all races. The LTFU rate was calculated to be 0.5% per year. At the end of the first year of the study the cumulative loss (death + LTFU) is expected to be 0.8% and by the end of year 12 it is expected to be 33.2%.

f. Other Factors

No lag time to supplement effectiveness is posited; such a lag time would have little effect on power because we are assuming a very low prostate cancer incidence rate in the first two years of the study.

It is assumed that the supplements being tested do not change the sensitivity or specificity of PSA or DRE, which could bias the diagnosis of prostate cancer. Sample size estimates are for the primary endpoint only. No adjustments have been made for multiple outcomes, such as prostate cancer-free survival, incidence or death from other cancers, or cardiovascular survival.

11.2 Sample Size Calculation

Based on the reported reductions in prostate-cancer incidence achieved by selenium and vitamin E, approximately two-thirds and one-third respectively, the target risk reduction is conservatively estimated to be 25%. For the factorial design, the detectable risk reduction is 25% for a single supplement relative to placebo with an additional 25% reduction for the combination relative to an effective single supplement.

The overall alpha level for the study is 5% (two-sided). Under the assumptions stated, the total sample size is 32,400 with randomization of 8,100 men to each of the four intervention arms. Under the assumed conditions, the median time under observation is estimated to be 8.8 years.

The estimated power for the pre-specified comparisons is as follows:

Comparison	Baseline Incidence	Relative Risk Reduction	Power
Single supplement vs. placebo	PCPT/SEER	25%	96%
Placebo vs. combination	PCPT/SEER	44%	> 99%
Effective single supplement vs. combination	0.75 x PCPT/SEER	25%	89%

A drop-in rate of 15% reduces the power to 92% for the comparison of placebo to single supplement and 82% for placebo or effective single supplement vs. combination.

The expected number of prostate cancer cases under the alternative hypothesis is as follows:

Supplement	Number at risk	Proportion of men diagnosed with Prostate cancer	Number or Prostate cancers detected
Placebo	8100	.066	533
Vitamin E	8100	.050	403
Selenium	8100	.050	403
Vitamin E + selenium	8100	.038	304

11.3 Analysis Plan

The primary analysis will consist of five pre-specified comparisons of prostate cancer incidence: vitamin E vs. placebo, selenium vs. placebo, combined vitamin E plus selenium (combination) vs. placebo, combination versus vitamin E, combination vs. selenium. These comparisons will allow for a meaningful analysis of the study results whether or not there is an interaction between vitamin E and selenium. Five interim analyses and one final analysis are planned.

a. Interim Analyses

Five interim analyses are planned occurring at 5, 7, 9, 10 and 11 years after the first participant is randomized. The percent of the total number of expected prostate cancer events at these analyses is 14%, 35%, 61%, 74% and 88% respectively.

Consideration will be given to reporting the study at each of these analyses. For each interim analysis, testing of the null hypotheses will be done at a one-sided level of .0005. In addition, the alternative hypothesis of a 25% reduction in prostate cancer incidence will be tested at a one-sided level of .0005 using an extension of the log rank test that allows for testing a relative risk not equal to 1.

b. Final Analysis

The final analysis will be completed within 6 months of the closure of the trial. The log-rank test will be used for each of the five pair-wise comparisons. Tests for interactions between vitamin E and selenium will also be performed.

A Bonferroni factor of five will be utilized to preserve the overall two-sided 5% alpha level while testing five pair-wise comparisons. Each individual test will be at a two-sided 1% alpha level.

c. Secondary Endpoints

The power to look at a difference in all cancer incidence is greater than 90%. There is limited power to look at survival (overall, cancer free, prostate cancer free, colon cancer free, lung cancer free, or cardiovascular) or to look at lung or colon cancer incidence. These analyses will be done using the log rank statistic.

Additional analyses, such as a main effects analysis and assessing the role of smoking and the effect of anti-oxidants on prostate cancer risk, will be performed.

d. Study Monitoring

The actual recommendation to terminate accrual early or to report results early will be made by the Data and Safety Monitoring Committee (DSMC). In addition to a relative risk reduction, the DSMC will consider overall survival, adverse events and other factors when making recommendations. Recommendations of the DSMC are reviewed by the Steering Committee who will make the final decision to terminate accrual early or to report results early.

It is possible that only specific arms of the trial will be closed and that the trial may continue with fewer than four arms.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

a. All pathologic specimens of the prostate leading to a diagnosis or suspicion of prostate cancer or high grade PIN (Grades 2 and 3) must be sent to the SELECT Pathology Review Laboratory for confirmation of diagnosis.

b. Instructions for preparation and submission of materials and a list of materials are described in Appendix 19.3 and the SELECT Study Manual.

Designated Study Sites may also participate in ancillary morphologic and biomarker studies. With the participants' consent, samples that will contribute to these studies will come from the material submitted for confirmation of diagnosis and a control sample of specimens from prostate procedures resulting in a benign diagnosis.

See Section 7.13 for pathology data collection process at the Transition Visit and after transition to centralized follow-up.

13.0 REGISTRATION GUIDELINES

Registration and randomization procedures are specified in the SELECT Study Manual.

14.0 DATA SUBMISSION SCHEDULE

Detailed data completion and submission procedures and schedule are found in the SELECT Study Manual.

15.0 SPECIAL INSTRUCTIONS

Detailed instructions for collecting and submitting specimens are found in the SELECT Study Manual.

15.1 Blood will be collected from all subjects at the time of randomization and at the 5 year annual visit and for those with prostate cancer at the Transition Visit (with the participant's consent).

15.2 A random sample (6%) of participants from designated study sites will be participating in measuring serum levels of vitamin E and selenium for adherence at 6 months, 1, 2, 4, 6, 8 and 10 years after randomization.

15.3 All potential participants who consent to submission of toenail samples will be required to allow their toenails to grow and not to use selenium-containing shampoo for one week prior to their randomization visit. Small samples will be collected from each toenail (with the participant's consent).

15.4 Materials sent for pathology review per Section 12.1 and 19.3 will be banked (with the participant's consent) for future studies.

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).

Supplement Accountability

For each supplement supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study supplement supplies must be maintained. Supplement 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 supplement is dispensed, the date(s) and quantity of supplement dispensed to the participant, and the date(s) and quantity of supplement 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. Pharmacies have been sent Study Supplement destruction letters on 11/6/08.

Adverse Experiences

Any unexpected or serious adverse experience, if deemed Study Supplement-related, must be reported within 24 hours of discovery to the Southwest Oncology Group Operations Office Serious Adverse Event (SAE) representative (210/450-8808), who will obtain information on the event. Depending on the nature of the reaction, the AE representative will advise further. See guidelines on next page. All deaths must be reported immediately to the AE representative

unless considered definitely not Study Supplement-related. 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 SELECT 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 must be 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 the investigator's written medical judgment as to the attribution of the adverse experience to Study Supplement(s) (i.e., "probable", "possible", "unlikely" or "unrelated").

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

GUIDELINES FOR REPORTING SERIOUS ADVERSE EVENTS (SAEs)
OCCURRING WITH VITAMIN E AND SELENIUM ON **S0000**

1. **WITHIN 24 HOURS OF FIRST KNOWLEDGE OF THE EVENT CALL THE OPERATIONS OFFICE AT 210-677-8808. THESE GUIDELINES ARE APPLICABLE ONLY UP TO 30 DAYS FOLLOWING THE LAST DOSE OF STUDY SUPPLEMENTS.**

2. WITHIN 10 DAYS, SEND TO THE OPERATIONS OFFICE

   a) The original, signed SELECT Serious Adverse Event Report (Form 409, available under "As Needed Forms" on the SELECT Workbench)
   b) Copies of clinical data documenting the adverse event
   c) IRB notification documentation
   d) Any other data requested during telephonic report.

3. IN ADDITION, FOLLOW THE GUIDELINES BELOW

   All Grades 3 - 5 Unexpected Reactions and Grades 4 - 5 Expected Reactions, according to NCI CTC Version 2.0. Criteria, must be reported as SAEs. Hospital discharge summaries and death certificates will be submitted for evaluation.

   For grading reactions, see the NCI Common Toxicity Criteria version 2.0: Appendix 19.1.

   The adverse event should be documented on the Southwest Oncology Group SELECT Adverse Event Report form (Form 409, available on the SELECT Workbench) and mailed to the following address, along with supporting documents:

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

   Expected toxicities are listed in the Drug Information or Background sections or in the model Informed Consent Form in the protocol.

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

   Reactions judged definitely not Study Supplement-related should not be reported. All deaths while on protocol or within 30 days after last taking Study Supplements must be reported, unless considered definitely not Study Supplement-related. Any death more than 30 days after discontinuing Study Supplements which is felt to be Study Supplement-related must also be reported. **A report shall be submitted if there is a reasonable suspicion that the toxicity is at least possibly related to the Study Supplement(s).**

   Reports of all Grades 3-5 Unexpected Reactions and Grades 4-5 Expected Reactions determined to be at least possibly related to either of the Study Supplements will be forwarded from the Operations Office to the FDA (as per the Code of Federal Regulations, 21 CFR 312.32) and to relevant drug companies.

4. Serious Adverse Event (SAE) Reporting During Follow-Up

In the unlikely event that an adverse event *with attribution of possible, probable, or definite* relationship to study supplement(s) occurs later than 30 days after the last dose of protocol-prescribed study supplement, it should be reported as follows:

- Grade 3-5 events - submit Form 409 including explanation of rationale for the attribution of possible, probable, or definite, and supporting clinical documentation within 10 calendar days of learning of the event.

Events with attribution of unlikely related or unrelated to study supplements do not require expedited reporting as SAEs. Grade 1 or 2 events do not require expedited reporting as SAEs. For required routine follow-up reporting of side effects/adverse events, see Form 203.

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18.0 MASTER FORMS SET

NOTE: All forms to be utilized for this study will be available via the SELECT Workbench at http://swog.org. Forms completion and submission guidelines are found in the SELECT Study Manual.

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

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 patient may be registered to this study.

Readability Statistics: Flesch Reading Ease 61.8 (targeted above 55)
Flesch-Kincaid Grade Level 8.7 (targeted below 8.5)

S0000, Selenium and Vitamin E Cancer Prevention Trial (SELECT)

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.

You are being asked to take part in this study because you are a healthy man and have never been told that you have prostate cancer. African American men who are of age 50 or older are eligible. Men of other ethnic groups aged 55 or older are eligible. The reason for this age difference is that prostate cancer appears at younger ages in African American men than in men of other ethnic groups.

WHY IS THIS STUDY BEING DONE?

Prostate cancer is the cancer (aside from skin cancer) found most often in U.S. men. Most men with prostate cancer do not die of this disease. Five-year survival rates are high due to early detection. However, even non-fatal prostate cancer can hurt your quality of life. For example, prostate cancer can cause sexual problems, urinary problems, pain in the bones, and pain in the lower back during bowel movements or during ejaculation.

The purpose of this study is to compare the effects (good and bad) of the study supplements. The supplements are selenium (*L*-selenomethionine), vitamin E (alpha-tocopherol), selenium plus vitamin E, and placebo (a pill containing no active substances). We want to see whether the supplements, other than the placebo, can prevent or reduce the occurrence of prostate cancer.

[Note to Institution: Remove the next paragraph if your site is not participating in the Health Related Quality of Life (HRQL). Participants include all CCOPs and selected VACSP sites.] *(5/25/01) (2/14/02)*

We also want to find out what the quality of life is like for men in this study. You will fill out forms to explain how you feel. It is very important to have your view about how you have been feeling while you are in the study. This is especially important because you are healthy and this study is being used for

possible prevention of cancer rather than as a treatment for a disease. By completing a form regularly, you will help describe the effect of this study on your quality of life.

In past studies of selenium's effects on other cancers, possible effects on reducing prostate cancer were found. However, a large study looking at the effects of selenium on prostate cancer has never been done. In past studies of vitamin E, it has also been linked with reduced prostate cancer. Again, a large study looking at the effects of vitamin E on prostate cancer has never been done. Past studies focused on effects on other types of cancer.

No studies looking at the effect of using both selenium and vitamin E have been done. Based on past studies using other agents as well as the two supplements we are testing here, we believe that men may get an added benefit from using these two supplements together.

While a formal study testing the effects of these supplements on preventing prostate cancer has not been done, the benefits of taking these supplements is strongly suggested. Please be aware that you have a twenty-five percent chance (1 in 4) of being assigned to receive neither of these supplements (placebos only). *(Paragraph added 5/25/01)*

The main purpose of this trial is to learn more about prostate cancers in healthy men that are found as part of regular medical care. We want to know whether the study supplements can prevent or decrease these cancers.

Optional Projects

We would also like to store samples of your blood, toenail clippings and tissue for use in future research. These studies might include genetic studies and nutritional studies related to cancer and other diseases that are common in your age group. None of these would be of direct benefit to you, but could help us learn about other ways to prevent cancer.

Giving blood, toenail clippings or tissue for future research is up to you. You may show whether you want to have these samples collected and stored by checking the box(es) at the end of this form. *(5/25/01)*

(Paragraph deleted 5/25/01)

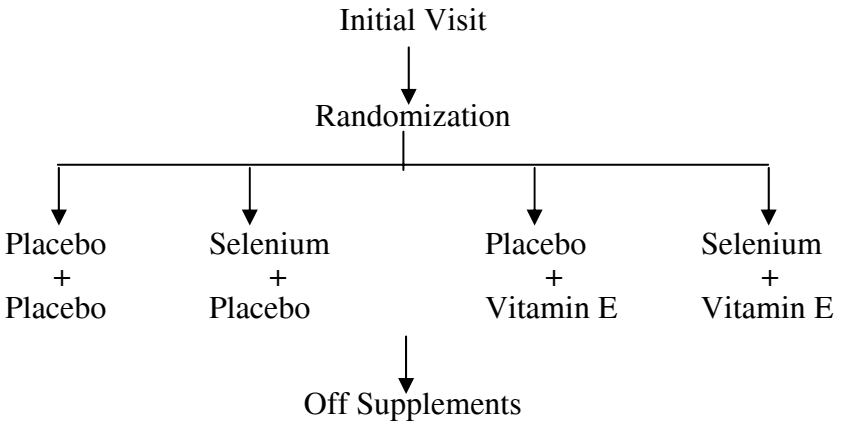
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 32,400 men will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

This study has four study groups. One group will receive two placebos (no active medication), a second group will receive selenium and a placebo for vitamin E, another will receive vitamin E and a placebo for selenium, and the fourth group will receive selenium and vitamin E. One placebo pill will look and taste the same as the selenium pill, and the other placebo pill will look and taste the same as the vitamin E pill.

You will be "randomized" into one of these four study groups. This means that you are put into a group by chance. It is like flipping a coin. Neither you nor the researcher will choose or know what group you will be in. A computer will assign the groups so you will have an equal chance of being placed in any group.



You will take two pills daily, one from each of two bottles. This will be continued for seven to twelve years (depending on when you entered the study). ***(All treatment on the study ended effective 10/23/08.)*** *(11/12/08)* At the end of the study, all participants will be told which group they were in. (Participants may also be told which group they were in if there is a medical need to know.)

It is important to have all four of these study groups to study the effects of vitamin E and selenium. Thus we ask if you take part in this study, that you only take the supplements of vitamin E and selenium we supply. We also ask that you stop taking any other supplements (including multivitamins) containing vitamin E or selenium. We will provide you (and your significant other, if you wish) with multivitamins made for this study. These are very similar to multivitamins you can buy in stores, but were made without vitamin E and selenium. We ask that if you desire to take multivitamins, you use only these multivitamins provided during the study. You may want to ask your doctor about taking these multivitamins. The study does not require that you take them.

If you take part in this study, you will have the following tests:

- During the first year, you will have a randomization visit and then will be contacted at three and nine months by phone to see how you are doing. The phone calls should last about fifteen minutes. At the randomization visit you will be asked to fill out a form which asks about your diet and vitamin use. *(5/25/01)*

- You will have office visits every six months and have your remaining pills counted. You will receive a limited medical exam every year. If you wish you may also have a yearly exam of your prostate (digital rectal examination). If you wish you may also have a yearly blood test (prostate specific antigen-PSA) to look for evidence of prostate cancer. You will be given a separate brochure to provide you with background on these tests. These office visits should take less than an hour, but time frame will depend on the amount of testing you wish.

- During this study you may have to have surgery or a biopsy on your prostate. If the tissue from the surgery is either suspicious for cancer or has pre-cancerous changes (high grade prostatic intraepithelial neoplasia-PIN), tissue samples will be sent to a SELECT central laboratory to confirm this.

*[**Note to Institution**: Remove the next paragraph if your site is not participating in the serum level adherence assessment.]*

- You will also have blood drawn at some follow-up visits to test the level of vitamin E and selenium in your blood. This blood draw will be done at randomization and at six months, one year, two years, four years, six years, eight years and ten years after you begin the study. Participants who are known to have an infectious disease such as HIV or hepatitis will not be asked for their blood sample. *(2/14/02)*

***[Note to Institution**: Remove the next paragraph if your site is not participating in the Health Related Quality of Life (HRQL). Participants include all CCOPs and selected VACSP sites.] (5/25/01) (2/14/02)*

- You will be asked to answer quality of life questions before you are assigned to your study group. The Nurse/Clinical Research Associate at your institution will give you directions for filling out these forms. You will be asked to answer these questions several times to help us see what kinds of changes happen over time. You will be asked to answer these questions during your visits on years one, three, five and seven.

Optional Projects

Even if you choose to take part in this study, the following projects are *optional*, and require your extra consent. You may show whether you wish to take part in *any* of these by checking a box at the end of this form. *(5/25/01)*

1. *(contact database deleted 11/21/05)*

2. The activities listed below involve giving blood, toenail clippings, and tissue for future study. The blood and toenail clippings will be collected at the time of randomization.

   - *If you agree*, four teaspoons of blood will be drawn and sent to a central storage space for use in future research.

   - *If you agree*, toenail clippings will be sent to a central storage space to look at the amount of selenium in your body. (When you take selenium, higher levels of selenium collect in your toenails.)

   - *If you agree*, prostate tissue samples which are taken for medical reasons and sent to a central storage space (as explained on the previous page) may be kept for future research. At some research sites, prostate tissue samples without cancer may be sent *if you agree*. *(5/25/01)*

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for seven to twelve years. This will depend on what year of the study you started. If you started in the first year you will be in the study for about twelve years. If you started in the fifth year of the study you will be in the study for about seven years.

The researcher will take you off this study (i.e., you will stop receiving supplements) if you develop prostate cancer. If this happens, we ask you to keep making clinic visits every year and/or respond to phone calls. We would like to keep track of your health until the study is over.

You may also stop receiving supplements for any of the following reasons. The side effects of the supplements are too risky for you (see "What are the Risks of the Study, below.). You stop coming in for required visits. New information about the supplements comes out that suggests the supplements will not work or will be unsafe for you. It is unlikely, but the study may be stopped early due to problems with study supplement supply or lack of funding.

You may remove yourself from the study at any time for any reason.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Many side effects go away shortly after the pills are stopped. In some cases side effects can be serious or long lasting or permanent.

Most people believe that vitamins and food supplements have few and mild side effects. However, the doses used in this study are higher than the recommended daily requirements for selenium and vitamin E.

Placebo

These pills do not contain any active ingredients. These pills will look just like the pills containing vitamin E or the pills containing selenium; however, there should not be any side effects. The selenium-matched pills contain an inactive filler (dicalcium phosphate) and the vitamin E-matched pills contain soybean oil. *(2/14/02)*

If you have any difficulty taking soybean products, please discuss this with your doctor. *(2/14/02)*

Selenium

Selenium is found in many foods. The dose of selenium for this study is not expected to cause you any side effects. However, long term use of selenium at higher doses has been known to cause mild nausea, garlic breath (or "bad breath"), hair or nail changes, cough (symptoms of the common cold), bronchitis, dizziness, weakness, skin redness or rash, irritability and tiredness. One study did report an increased risk of non-melanoma skin cancer (particularly squamous cell skin cancer) with selenium use in patients who had previously had this disease. *(1/14/04)* **Removing selenium supplementation can reverse side effects. There may also be other side effects that we cannot predict.**

Vitamin E

No serious side effects have been linked to the use of vitamin E in the doses used for this study. One study did report an increased risk of stroke among male smokers taking this vitamin; however, this risk was seen only in male smokers who already had uncontrolled high blood pressure.

Combination

Based on prior studies, the combination of selenium and vitamin E is not expected to cause extra side effects. We do not expect either different side effects or more frequent or severe side effects than with each supplement given alone. As with the use of selenium and vitamin E alone, there also may be side effects from the combination that we cannot predict.

Samples of Tissue, Toenail Clippings and Blood Banking

There are very few risks to you.

The blood draw could cause minor pain and/or leave a bruise.

There is a remote risk that release of information from your research record would affect applications for insurance or jobs by 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 tissue, blood or toenail sample. Any research information about you is kept private.

If further projects are planned that require use of samples which can be directly linked to you, we will contact you and ask for this consent. (If you do not want to be contacted for future studies but would like to give your permission for these studies you can check a box at the end of this form.)

Genetic studies are very complex. They require many cells to explore how genes may affect the risk of prostate cancer. A small amount of your white blood cells may be "grown" in a laboratory to develop a "cell line" that can be used for this research.

You should face no extra risks beyond those mentioned above if your white blood cells are "grown" in the laboratory to develop a "cell line" for use in genetic research.

For more information about risks and side effects, ask the researcher or contact (NAME)_____.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

The main benefit this study hopes to provide is knowledge. We hope to find knowledge that will be useful to other men in the future. If the study shows that any of the study groups has had a good result, the people in the study who take that supplement(s) would receive this benefit. But the use of vitamin E and/or selenium supplements has not been shown to reduce or prevent prostate or other forms of cancer. So there is no guarantee that you will receive any benefit from being in the study. The researchers feel that being in this study will give you at least as good a chance of preventing prostate cancer as you might expect from other supplements or drugs.

The possible benefits of being in the study are the same as taking selenium and/or vitamin E without being in the study.

(Paragraphs deleted 1/20/03)

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

You may choose to be in other studies looking at other ways to prevent prostate cancer, if you are chosen to take part in such studies. One large study has shown that finasteride is effective in preventing prostate cancer in some men. However, men on the study who got prostate cancer while taking finasteride experienced a slightly higher rate of high g
rade tumors.
(1/14/04)

Some vitamin companies are selling selenium and vitamin E, as well as other nutrients, as supplements for prostate health. You may buy these supplements at your own expense without being on the study. *(sentence deleted 2/14/02)*

Please talk to your regular doctor about these and other options.

No one knows if any of these supplements prevents or helps prevent prostate cancer. *(1/14/04)*

WHAT ABOUT CONFIDENTIALITY?

The data about your participation in this study will be kept secret. It will be used only for research, as allowed by state and federal laws. As genetic research may find genetic knowledge about you, this knowledge will be kept secret to the full extent allowed by law. Your blood, toenail clippings, tissue and health information will not be labeled with your name. No one who works with these samples will have access to your name. Your name and any identity information will not be used in any reports.

Individual results about research done with your blood, toenail clippings or tissue will not be routinely given to you or your doctor. *(2/14/02)* These reports will not be put in your health record. The research will not have an effect on your care. You can be in the main study without having your blood, toenail clippings or tissue stored for future studies.

We cannot guarantee complete secrecy. We may disclose your personal data if required by law. Your records for this study will be sent by facsimile transmission (FAX machine) or over the Internet directly into a central computer. It is possible (although unlikely) that your records could be sent to the wrong FAX machine in error. Records sent by computer will be sent using current Internet security.

Groups that may inspect and/or copy your research records include: the National Cancer Institute; the Food and Drug Administration; the makers of the vitamin E, selenium and placebo pills for this study, and the Southwest Oncology Group.

If we publish the information we learn from this study, you will not be identified by name or in any other way.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance. *(5/25/01)* Added costs may be due to side effects, finding cancer or other diseases at your exam or from blood or tissue samples. *(5/25/01)* For example, your doctor may suggest a biopsy if you have an abnormal prostate exam (digital rectal examination-DRE) or blood test (prostate specific antigen-PSA). These costs are discussed further below. Please ask your nurse or doctor about any expected added costs. *(5/25/01)*

If you get hurt or sick from being in this study, emergency medical treatment is available. This treatment will be provided at the usual charge. No funds/funds have been set aside to pay you if you get hurt or sick. *(Local institutions must choose the option that best fits the hospital's situation)*

You or your insurance will be charged for medical care and/or hospital care if needed. While the PSA test (if you desire it) will be reimbursed at a set rate every year while you are on this study, other medical costs (including biopsy costs, if a biopsy is required) will be charged to you or your insurance. The PSA test that helps to find out whether you can be in this study will be (charged in the usual way/provided at a reduced rate). *(Local institutions must choose the option that best fits the hospital's situation). (5/25/01)*

You will receive no payment for taking part in this study. Getting to the study site is your own responsibility, and at your own cost. *(Local institutions may update this information as best fits their situation.)*

The cost of keeping research records will be paid by the study. The research requires that you receive certain standard tests, exams and office visits. These standard tests, exams and office visits will be (charged in the usual way/provided at a reduced rate). (*Local institutions must choose the option and outline in detail the participant financial responsibilities that best fit the hospital's situation) (5/25/01)*

The investigational supplements selenium, vitamin E and placebo will be provided free of charge for this study. A specially made multivitamin will also be provided for you and (if desired) your significant other free of charge for this study.

There will be no cost to you for any blood, toenail clippings or tissue stored by the Southwest Oncology Group.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may withdraw all or any part of your consent to be in the study at any time. You may choose not to receive further supplements. You may choose to withdraw from any extra project. *(11/21/05)* Leaving the study will not result in any penalty or loss of benefits to which you are entitled. However, before you decide to stop being in the study, we would like you to talk to your study doctor and your regular doctor. *(paragraph edited 1/14/04)*

If you choose to stop taking supplements, and later wish to return to the study (in the same study group), you can. However, if you stopped taking supplements because the supplement(s) caused health problems for you or others, you may not be allowed to take more supplements. If you stop taking your study supplements for any reason, you can still be a part of this study. This means you can continue clinic visits and provide information about your health by completing forms, being available to answer questions, or allowing us access to your medical records. *(1/14/04)* We would like to continue to watch your health whether or not you are taking supplements.

You may be in the Selenium and Vitamin E Cancer Prevention Trial and yet decline to have blood, toenail and tissue samples stored for future research. Further, if you first decide to have these samples stored for research, but later change your mind, you may do so by giving written notice of this to (**principal investigator**) at the (**participating institution**). The remains of your samples will then be destroyed. Your decision will not affect your care.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research. They will review this data throughout the study. Their review will not be given to you or your doctor. You will not know the results of their review unless it is clear that the supplements are working, or that they are causing serious harm.

If there is important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study, you will be informed and may be asked to renew your consent to participate.

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*.

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.

1. Participant _____ Date _____

2. Details regarding participation in the contact database project project were deleted 10/24/05 as this project is no longer being done in the SELECT study. *(added 11/21/05)*

Also, document your willingness to take part in additional studies by answering items 3 and 4 below. Your participation in any additional study is entirely voluntary and in no way effects your participation in SELECT. *(sentence updated and 3 - 4 added 5/25/01) (2/14/02)*

3. Sub-studies requiring active participation *(#3 updated 2/14/02)*

Some men will be asked to participate in special sub-studies requiring their <u>ACTIVE</u> participation.

I agree to be contacted with information about special sub-studies.

☐ **Yes** ☐ **No** **Initials: _____**

4. Sub-studies on stored specimens

We would also like to store your samples of blood, toenail clippings and tissue for further research. These studies might include genetic studies, and nutritional studies related to cancer and other diseases that are common in your age group. None of these would be of direct benefit to you, but could help us learn about other ways to prevent cancer or other health problems. Participants who are known to have an infectious disease such as HIV or hepatitis will not be asked for their blood sample. *(2/14/02)*

Please check box A or B or C and initial as indicated. *(2/14/02)*

A. ☐ I refuse to allow my specimens to be collected. *(5/25/01) (2/14/02)*

Initials: _____

OR

B. ☐ **I consent to collection of my blood, toenail clippings and prostate tissue specimens and to <u>ALL</u> future studies involving the use of my specimens. It is unnecessary to contact me further regarding studies on my stored blood, toenail clippings or prostate tissue specimens.** *(5/25/01) (2/14/02)*

Initials: _____

OR

C. ☐ **1.** **I specifically consent to the collections of the following specimens, the use of the blood and toenails in determining baseline nutrient levels, and the review and storage of prostate tissue:** *(2/14/02)*

Blood ☐ **Yes** ☐ **No** **Initials:** _____

Toenails ☐ **Yes** ☐ **No** **Initials:** _____

Prostate Tissue ☐ **Yes** ☐ **No** **Initials:** _____

2. **I specifically consent to the use of my stored specimens for the following types of research:** *(2/14/02)*

a. **My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.** *(2/14/02)*

☐ **Yes** ☐ **No** **Initials:** _____

b. **My specimens may be kept for use in studies about other health problems (for example: diabetes, Alzheimer's disease and heart disease).** *(5/25/01) (2/14/02)*

☐ **Yes** ☐ **No** **Initials:** _____

c. **Someone from the Southwest Oncology Group may contact me in the future to ask me to take part in more research (outside of the research indicated in questions C2a and C2b above) involving the use of my stored specimens.** *(5/25/01) (2/14/02)*

☐ **Yes** ☐ **No** **Initials:** _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

19.0 APPENDIX

19.1 This study will utilize the CTC (NCI Common Toxicity Criteria) version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). **All appropriate treatment areas should have access to a copy of the CTC version 2.0.**

19.2 Staging Criteria for Prostate Cancer

19.3 Pathology Review and Storage of Materials for Ancillary Studies

19.4 Quality of Life Substudy

19.5 Participating Study Centers and Sites

19.6 Model Informed Consent - Collection and Storage of Additional Blood Specimens

19.7 Informed Consent – Centralized Extension of Follow-Up

19.8 Alternatives for Transition to Centralized Follow-Up (Plans B and C)

APPENDIX 19.2

Clinical Staging. Primary tumor assessment includes digital rectal examination of the prostate and histologic or cytologic confirmation of prostate carcinoma. All information available prior to first definitive treatment may be used for clinical staging. Imaging techniques may be valuable in some cases; TRUS is the most commonly used imaging tool. Tumor found in one or both lobes by needles biopsy, but not palpable or visible by imaging is classified as T1c. Considerable uncertainty exists about the ability of imaging to define the extent of a nonpalpable lesion (see definition of T1c below). For research purposes, investigators should specify if clinical staging into the T1c category is based on DRE or DRE plus TRUS.

STAGING CRITERIA

AJCC TUMOR (T), NODE (N), METASTASES (M) CLASSIFICATION
PROSTATE CANCER (5th ed., 1997)

DEFINITIONS

Primary Tumor, Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable nor 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	Tumor confined within prostate*
T2a	Tumor involves one lobe
T2b	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

Regional Lymph Node (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a regional lymph node or nodes

Distant Metastasis (M)***

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

---

* Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably 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 is used. pM1c is most advanced.

APPENDIX 19.3

Pathology Review and Storage of Material for Ancillary Studies

Introduction:

a. Central pathology review is required for all pathologic specimens of the prostate that lead to a diagnosis of:

- Prostate cancer
- Suspicion/atypical diagnosis
- High Grade PIN (Grades 2 or 3)

b. These samples may come from a prostate biopsy, a transurethral resection of the prostate (TURP), a cysto-prostatectomy, a radical prostatectomy or any other procedure resulting in prostate tissue.

c. Ancillary morphologic and biomarker studies will be conducted. Samples that will contribute to these studies will come from the material submitted for endpoint review (with additional patient consent given for future tissue use) and a random control sample of specimens from prostate biopsies resulting in a benign diagnosis. The latter will be identified from Study Sites and participants that have expressed an interest and ability to participate in such research.

Obtaining necessary material:

To insure that the necessary material for pathology review needed for endpoint confirmation is available, the SELECT principal investigator in a participating Study Site is strongly encouraged to introduce the SELECT protocol to the person in charge within the institution's Department of Pathology prior to its activation. It should be explained that the participant consent allows for the review and storage of the material, and that the pathology efforts of case retrieval, sectioning and shipping are appropriately compensated. Coordination with the Institutional Review Board (IRB) and the risk management office may also be required.

Throughout the course of the study, communications between the chair of the Pathology and Biomarker Committee and pathologists at Study Sites will continue. It is the commitment of the Pathology and Biomarker Committee and the Study Coordinators of SELECT that borrowed slides, blocks or frozen samples will be available to the Study Site should a participant care issue or a medico-legal concern arise.

If necessary, the chair of the SELECT Pathology and Biomarker Committee, Dr. Wael Sakr, is available by mail, telephone, FAX and e-mail at the addresses and numbers on the face page of this protocol.

Submission of materials:

a. To allow for maximum flexibility four "levels" of materials will be accepted. The minimum submission requirement for confirmation of the prostate cancer endpoint is considered Level 1. Level 2 submission provides material for storage and Level 3-4 submission provides material for storage and future utilization in ancillary studies. For participants know to have bloodborne infectious diseases such as HIV or hepatitis, please submit at Level 1 or Level 2 only. Monetary compensation will be increasing from Level 1 to 4 due to the complexity of the efforts associated with forwarding the material.

Level	Requirement
1	H&E (hematoxylin and eosin) diagnostic slides
2	H&E diagnostic slides + a minimum number of blank "unstained" slides
3	H&E diagnostic slides + representative paraffin blocks
4	H&E diagnostic slides + frozen tissue for storage in a -70°C freezer

Radical prostatectomy specimens: For participants who have a confirmed diagnosis of cancer and have a radical prostatectomy, additional material may be available and submitted for morphologic evaluation and marker studies. Study sites participating in this additional submission will be compensated. (Details for submitting samples from radical prostatectomy specimens are provided in the SELECT Study Manual.)

b. Within 30 days of the diagnosis of prostate cancer, high Grade PIN or suspicious/atypical findings, submit the requested materials as outlined in the SELECT Study Manual:

c. Ship materials using the established pre-paid Federal Express account number to the SELECT Pathology Review Laboratory as outlined in the SELECT Study Manual.

Processing of materials at the Pathology Review Laboratory:

Upon receipt, the sample will be logged into a computerized data base and appropriately stored (frozen samples will be immediately transferred to a -70 C ultrafreezer). The material will be checked with respect to completeness, integrity, compliance with harvesting and packaging requirements, etc. An acknowledgment of receipt will be sent to the Study Site via FAX. Any problem with the submission will be indicated.

The sample will then be assessed for its suitability to fulfill the needs of all proposed ancillary studies.

For the ancillary studies, a hematoxylin and eosin stained section will be generated from every tissue sample and block submitted. The H&E slides will be examined by the SELECT pathologist to assess the amount of tissue, its microscopic make up, the fixation and/or freezing quality of the sample, and its suitability for a specific study modality such as image analysis biomarker staining, etc. The H&E stained slides or the records indicating their content will be reviewed prior to the initiation of any of the ancillary studies.

When paraffin blocks are available, blank slides for immunohistochemical staining will be generated within a week from the anticipated staining day to insure the integrity of antigenicity and the consistency of staining results.

Review of materials:

Upon review of the materials, the sample will be categorized into one of the following 4 diagnostic categories:

1. Benign (includes Grade 1 prostatic intraepithelial neoplasia (PIN))

2. Prostatic adenocarcinoma

3. High grade prostatic intraepithelial neoplasia (PIN) (Grades 2 - 3)

4. Atypical/suspicious findings

The results of the review will be faxed to the Study Site. In addition, it will be noted whether there is agreement or a minor or major diagnostic discrepancy with the Study Site pathologist, or whether further material is needed for review.

To resolve major discrepancies, an additional 1 - 2 pathologists from the Pathology and Biomarker Committee will review the sample. The final diagnosis will be the result of the majority opinion.

APPENDIX 19.4

Quality of Life Substudy

Research Aim

To make five comparisons associated with four chemopreventive arms for two measures of HRQL: the SF-36V Physical Component Scale score, and the SF-36V Mental Component Scale score.

Rationale

Quality of life is an important outcome measure to monitor in a trial with healthy participants who are asked to take a chemopreventive agent for a protracted period of time. Chemopreventive agents can have broad impacts on a participant's functioning as well as specific side effects associated with the agent. Health-related quality of life (HRQL) refers to a focus on areas of functioning that would be expected to be affected by a medical intervention, such as a chemoprevention intervention. *(37, 38)* That is, we restrict our HRQL assessment to basic domains of functioning such as physical, emotional, role, and social functioning.

An HRQL endpoint not only allows monitoring of effects of the chemopreventive agent on participant functioning but also communicates to participants that trial investigators are concerned enough about such effects to include their assessment as part of the trial design. A participant's expectations regarding the research team's concern for his well-being can affect willingness to enroll in a long-term trial. *(39)* In addition, with regular monitoring of HRQL data by the trial's Data and Safety Monitoring Committee (DSMC), trial investigators can be alerted to potential adherence problems if participants in one or both arms are reporting more negative effects on HRQL. An example of such feedback from the Prostate Cancer Prevention Trial (PCPT) was the DSMC's decision to release placebo arm sexual functioning data for baseline and the first two years of follow-up. These data indicated mild problems with sexual functioning at study entry with increasing problems reported over the two-year period. Since placebo arm participants were receiving an inactive substance not known to cause problems with sexual functioning, the reported increase in problems was likely related to aging or to other factors. This information was described in the participant newsletter, the Vanguard, and helped inform participants and support adherence to study requirements.

HRQL data also help characterize participants, which helps 1) interpret intervention effects or lack of effects, and 2) helps identify groups of participants to target in follow-up research. In the Prostate Cancer Prevention Trial (PCPT) evaluating finasteride versus placebo, we measured HRQL annually for seven years with the SF-36 Health Survey. *(40 - 45)* We described the baseline HRQL profile of men who were randomized to this trial. *(45)*

HRQL Sample

Since comparing the four arms of the trial for HRQL differences does not require the full 32,400 sample required for the prostate cancer incidence endpoint, we will select a subsample of participants from two major sources: all Community Clinical Oncology Program (CCOP) sites; and a sample of Veterans Affairs (VA) sites. Each sample strategy is discussed below.

HRQL Eligibility Criteria

The HRQL study has three eligibility requirements.

1. HRQL participants must be randomized from a CCOP institution or from one of the selected participating VACSP sites.

2. An HRQL participant must have literacy skills that enable him to read and complete a questionnaire and provide responses to items. Only participants who are considered completely unable to complete the questionnaire should be excluded. This determination is based on the investigator/CRA best judgment.

3. Participants must be able to complete the HRQL questionnaire in either English or Spanish. Participants who use a language other than English or Spanish are excluded from the HRQL study.

HRQL CCOP Sample

In the PCPT, CCOP trial sites contributed 7,141 of the 18,882 final randomized sample. To retain eligibility as a CCOP, a site must earn 50 cancer control credits per year. Therefore, cancer control credits can serve as an incentive to collect HRQL data. In addition, CCOPs are familiar with HRQL assessment, which has occurred in a number of cooperative group treatment trials as well as in prevention trials.

In the PCPT, participants from CCOP versus non-CCOP sites did not differ with respect to basic demographic data, nor did they differ with respect to SF-36 domain and summary scores. See Tables 1 and 2. For this reason, we believe that HRQL data provided by CCOP participants would not generate a biased picture of HRQL in the trial. In addition, CCOPs are familiar with HRQL assessment, which has occurred in a number of cooperative group treatment trials as well as in prevention trials. *(39, 52 - 54)* In SELECT we estimate that CCOP study sites will contribute approximately 10,000 participants for the HRQL study.

TABLE 1

PCPT
Participant Characteristics at Randomization
(Data as of 12/9/98)

	CCOP (n=7,141)	Non-CCOP (n=11,741)
	% Enrolled	% Enrolled
AGE		
55-59	30	30
60-64	31	31
65+	39	39
RACE		
White	94	91
Black	3	4
Other	4	4
HIGHEST EDUCATION LEVEL		
Grade School	2	1
Some High School	3	3
High School Graduate	16	14
Voc./Training School	6	4
Some College	23	26
College Graduate	17	16
Post Graduate Education	33	37
PSA		
≤ 1.0	49	48
1.1-2.0	35	36
2.1-3.0	16	16
INCOME (thousands)*		
<$10	.1	.2
$10-30	43	41
$30-50	47	50
$50-70	8	8
>$70	1	.8
PROSTATE CANCER IN 1ST DEGREE RELATIVE		
Yes	15	15
No	85	85
MARITAL STATUS		
Never Married	2	3
Divorced/Separated	7	8
Presently Married	86	84
Widowed	3	3
Marriage-Like Relationship	2	2

*Derived from zip code match to 1990 U.S. Census

TABLE 2

PCPT: SF-36 Data at Baseline for CCOP VS. Non-CCOP
(Data as of January 7, 1999)

	Non-CCOP	CCOP
SF-36*	(n = 11,741)	(n = 7,141)
MCS mean	54.9	54.9
Sd	6.1	5.9
med.	56.3	56.2
PCS mean	52.0	52.3
Sd	7.2	6.8
Med	53.8	54.1
	means	
GH (general)	81.0	81.6
HT (transition)	46.3	46.8
PF (physical)	86.7	87.4
RP (role-phys)	91.2	92.3
RE (role-emot)	94.3	94.6
SF (social)	94.5	95.0
BP (bodily pain)	81.8	82.6
VI (vitality)	71.1	71.0
MH (mental)	81.1	81.3

*Higher scores reflect better HRQL

HRQL VACSP Sample: In the PCPT ninety-one percent of non-CCOP participants were Caucasian whereas 94% of CCOP participants were Caucasian. Clearly neither type of institution provided sufficient variation in racial and ethnic background. Extensive effort was expended to obtain the overall 4% accrual of African American men and 4% of other minority men enrolled on the PCPT. In SELECT, we will be including selected VACSP sites to provide a more diverse base of participants from which to recruit for the HRQL ancillary study. These sites will be selected to increase the potential for accrual of large numbers of African American participants; a secondary accrual target is Hispanic men. These VACSP sites would be expected to contribute approximately 8,000 participants for the HRQL sample. Based on ongoing VACSP participation in studies such as the multi-site prostate cancer HRQL study, we would expect that approximately 25% to 40% of the VA participants in the HRQL sample would be minority (primarily African American participants). *(55)*

HRQL Questionnaire

In the PCPT, three patient-reported measures addressed different aspects of functioning. The SF-36 Health Survey provided a measure of eight domains of general functioning: physical, role associated with physical status, role associated with emotional status, social, and emotional functioning; fatigue; pain; health perceptions. *(40 - 44)* The SF-36 Health Survey was designed to measure the health status of individuals in the general population and individuals who have various chronic diseases and health conditions. It therefore is an appropriate measure for men volunteering to participate in a chemoprevention trial. It was sensitive to age (< 63 vs ≥ 63) and to the presence or absence of chronic health conditions such as diabetes, high blood pressure, and current smoking. *(45)* Normative data are available with which to compare trial participants to respondents in the general population. *(43 - 44)* The SF-36 Health Survey was used in the PCPT and the Breast Cancer Prevention Trial (BCPT). *(45, 52, 57)* In both the BCPT and PCPT, submission rates for the SF-36 Health Survey were excellent. *(45, 52, 56 - 58)* For example, year one PCPT assessments achieved a 97% submission rate for the SF-36 questionnaires. *(56)* At this point, all PCPT participants have completed at least 3 years on trial and for the third year assessments, submission rates are ≥ 90% (unpublished data).

We propose use of the SF-36V as the primary measure of participant-reported HRQL. *(46 - 49)* Veterans Affairs (VA) researchers modified the SF-36 to increase the precision and discriminate validity for the role functioning scales and the two summary scales for assessment of patients in the VA ambulatory care setting. The primary modification was to provide five-level response format instead of dichotomous (Yes/No) format for the SF-36V.

An important step in establishing a QOL instrument's feasibility, reliability, and validity is evaluating its psychometric properties in a broad range of clinical populations. Thirty-one percent of men with prostate cancer at two Veterans Affairs (VA) sites serving predominately low-income populations had ≤ sixth grade reading level. *(59)* To compensate for low literacy levels present in its patient population, the VA has successfully implemented a centralized phone bank, interviewer-assessment strategy as an alternative to self-administered HRQL questionnaires. *(60)* The feasibility, validity, and reliability of telephone-administered questionnaires were documented for this group of VA patients. Interviewer-administered HRQL data was associated with virtually 100% completion of questions by all participants, rates that are much higher than those reported with self-administered questionnaires. *(60)* In general, little is known about the HRQL of persons who are in lower socioeconomic strata and who have low literacy skills. The participation of VACSP sites will provide a group of participants with low literacy level and the ability to examine differences in report of HRQL based on literacy levels and method of data collection.

The VA modification of the SF-36 improved internal consistency reliability for the role functioning/physical problems scale and did not change for the role functioning/emotional problems scale; acceptable reliabilities hold in either case. *(48)* The modification also decreased the percentage of patients scoring at the ceiling and floor levels for the role functioning scale scores. *(48)* The factor structure for the SF-36V and SF-36 were similar, as were factor structures for the two summary scales created by each version. *(48)* Kazis et al. used the SF-36V in a sample with 23% African American patients. *(61)* However, psychometric data specific to the African American sample were not reported in this paper. A minor modification was the separation of the single SF-36 transition in health item ("Compared to one year ago, how would you rate your health in general now?") to two items for the SF-36V: "Compared to one year ago, how would you rate your physical health in general now?"; "Compared to one year ago, how would you rate your emotional problems (such as feeling anxious, depressed or irritable) now?". Scoring for the questionnaire does not involve the transition item(s).

The SF-36V differs minimally from the SF-36 (i.e., the only important change applies to the two role functioning scales) and the papers cited above indicate that the excellent measurement properties of the SF-36 have been maintained in the SF-36V. *(47)* Psychometric studies and papers reporting the use of the SF-36 with different minority groups are available and therefore can be informative when evaluating the appropriateness of the SF-36V for use with minority groups. *(62)*

Kazis et al. reported that race was not significantly associated with either of the two SF-36 summary scale scores in a study with VA patients; variables such as age, education, and income did predict one or both summary scores. *(63)* Two papers support equivalent measurement properties for the SF-36 when used with African American respondents. McHorney et al. reported that measurement properties (e.g., internal consistency reliability, inter-item correlations, scaling success rates [items correlating more highly with hypothesized scales than other scales]) met accepted standards in a number of subgroups, one of which was African American respondents. *(42)* Data completeness (i.e., missing responses to items) was lower for African American patients. However, the percentages of African American respondents for whom scale scores could be computed were ≥ 94% for the eight SF-36 scales. Internal consistency reliability ranged from .76 for the general health scale to .93 for the physical functioning scale; a coefficient alpha reflecting internal consistency reliability of ≥ .70 is considered acceptable. The fact that reliability and scaling properties for African American and Caucasian respondents are similar supports the fact that the two groups are treating/processing the items similarly, an important aspect of cultural appropriateness.

Johnson et al., reported that certain clinical and non-clinical variables were significantly correlated with SF-36 scores (gender, age, comorbidity, and cardiovascular functional status); these correlations were similar for African American and Caucasian patients with acute chest pain. *(64)* African American patients had lower scores on most of the SF-36 scales, but race did not predict SF-36 scores once cardiovascular functional status, other clinical factors, and socioeconomic status were included in multivariate models. Johnson et al. concluded that reliability and validity of the SF-36 were documented for an African American patient group and that SF-36 scales did not appear to be affected by cultural differences present in the two races. The authors further concluded that their results are reassuring regarding the use of the SF-36 with African American

respondents but noted that similar research is required to assess the cultural and measurement appropriateness of the SF-36 with other groups.

The Southwest Oncology Group has experience administering SF-36 scales to Hispanic patients. The SWOG QOL Questionnaire includes four of the SF-20/SF-36 scales. In a funded study we documented the equivalence of English and Spanish versions of the Southwest Oncology Group (SWOG) Quality of Life (QOL) Questionnaire in terms of a number of measurement properties. In addition, a graduate student and Research Assistant for the grant examined responses to two open-ended questions regarding 1) any aspects of QOL deemed important to the patient that were omitted from the questionnaire and 2) the aspect of health most affecting overall QOL. Most Hispanic patients with breast or prostate cancer did not identify any aspects of QOL that were not already included in the items. Hispanic breast cancer patients noted psychological health as most important while all other groups identified physical health as most important to overall QOL. It appeared that disease, the effects of treatment, and personal characteristics overwhelmed the influence of culture. We also conducted focus groups with different Spanish-speaking patients with breast or prostate cancer (i.e., not included in the data sample); these groups also did not identify areas that should be added to the questionnaire. These data have not been published but are described in a Final Report. *(65)* We conclude from these data that the SF-36 is culturally appropriate for Hispanic patients with cancer. Given use of a Spanish translation of the SF-36 in the PCPT to date, we do not anticipate cultural appropriateness problems with this ethnic group for SELECT.

We cannot document the appropriateness of the SF-36 for other ethnic and minority groups. However, Ware et al. have documented the use and scoring of the two summary scores for the SF-36 in ten Western European countries. *(66)* There is probably more accumulated data on use of the SF-36 with various language groups than almost any other HRQL questionnaire. *(62)* Given available data on the SF-36's use with various ethnic and minority groups, our experience with the SF-36 in the PCPT, and the SF-36V's close similarity to the SF-36, we are comfortable using the SF-36V in SELECT.

We will also include a single-item measure of global HRQL, the UNISCALE, a visual analogue scale (VAS) measure with two anchor points, "lowest quality" and "highest quality". *(50, 51)* The item was validated as a measure of overall HRQL. *(51)* Because of limitations posed by Teleform, we will rescale the UNISCALE as an 11-point scale, ranging from "0" ("lowest quality") to "10" ("highest quality"). Collins et al. reported that such scaling does not interfere with measurement properties. *(67)* In addition, since one purpose of including the UNISCALE is to examine its correlation with the two SF-36V summary scores, we have changed the "one week" (or "two week") time frame to a "past four weeks" time frame to match that of the SF-36V.

Toxicities will not be measured with patient-report scales; side effects of chemopreventive supplements will be tracked by usual toxicity rating scales administered by Clinical Research Associates (CRAs)/nurses at study sites. Diet will be addressed in a separate ancillary study. Lifestyles data, important for HRQL comparisons, will be collected as part of basic trial entry data requirements.

HRQL Assessment Schedule and Procedures

HRQL data will be collected prior to randomization and at years one, three, five and seven of the trial. Data will be collected at the annual clinic visits; participants can mail questionnaires to the SELECT site if a clinic appointment is missed or delayed. See SELECT Study Manual for details of questionnaire submission.

Statistical Power and Analysis Plan for the HRQL Ancillary Study

The basic HRQL hypothesis is one of equivalence between treatment arms. HRQL is included to monitor treatment arms for toxicities and side effects of long-term use of the two supplements. The HRQL sample size of approximately 9,200 participants is based on the expected CCOP registration of approximately 7,100 participants (based on PCPT CCOP accrual) and the addition of approximately 2,100 participants from 14 VA sites. This 9,200 sample size must be examined with respect to several factors affecting sample size. The four cells of the factorial would result in 2,300 participants per cell. The second factor is the hypothesized equivalence of HRQL in this trial; tests of equivalence require larger sample sizes to conclude that no differences exist. The third issue involves the role of multiple comparisons. There are five treatment arm comparisons

planned for SELECT: 1) vitamin E versus placebo; 2) selenium versus placebo; 3) combined vitamin E plus selenium (combination) versus placebo; 4) the combination versus vitamin E; 5) the combination versus selenium. There are also two SF-36 summary scale scores. Therefore, an alpha of .005 is required to conduct testing at an effective level of .05.

The manual for the SF-36 Physical & Mental Health Component Summary Scale (PCS and MCS) scores provides some insight on numbers of individuals required to detect differences on the two SF-36 summary measures. *(44)* For example, 801 participants are required to detect a one point difference (0.1 standard deviation [sd] units for the PCS and MCS standardized measures. More participants are required for comparisons involving the individual SF-36 scales. *(43)* For example, the Physical Functioning scale requires 1364 participants to detect a two point difference (equivalent to the .1 sd unit for the summary scale measure). Cohen describes a small effect as between .2 to .5 sd units, differences of .5 to .7 as moderate effects, and differences larger than .7 sd as evidence of large effects. *(68)* Therefore, for HRQL treatment arm comparisons in SELECT, we define equivalence as any effect less than .2 sd units on the two SF-36 summary scale scores (i.e., less than 2 point difference). The proposed sample size of 9,200 participants allows the detection of differences of less than two points and therefore supports our ability to conclude equivalence based on the above definition.

These PCS and MCS outcome measures will be compared at seven years for the five treatment arm comparisons. At 7 years, we will use t-tests to test the five comparisons associated with this design for each of the two HRQL outcomes. If distributions are not normal, we will use nonparametric procedures. Since the SF36V will be assessed at randomization, and at years 1, 3, 5, and 7, a second analysis approach will examine change over time including all data points. We will use a mixed linear model approach to test differences in the rate of change for the PCS and MCS for each of the five treatment arm comparisons. The presence of non-ignorable missing data can be a problem for analyses of change. However, given the excellent SF-36 submission rates for the PCPT and the fact that men in this trial will be basically healthy, we do not expect substantial amounts of missing data. *(45, 56)* Because of the healthy status of men who will enroll in SELECT, we do not have any basis for expecting radically different submission rates for SELECT. The longitudinal analysis will include adjustments for age and comorbidity. Tests in each of the two analysis sets will be conducted at α=0.005.

However, at the time of analysis, we will examine plots of cohorts of SELECT participants who have HRQL data (MCS and PCS summary scores) for varying numbers of scheduled assessments to see if those who fail to provide follow-up data show worsening scores at the time of their last questionnaire. We have used this procedure in the treatment trials with HRQL data. *(69)* We will also examine variables associated with missing data (e.g., on/off treatment, toxicity ratings, clinical status, etc.). If there is evidence of non-ignorable missing data, we will use an approach considered appropriate in this context, such as pattern mixture models. *(70)* We have employed pattern mixture models in a recent lung cancer trial. *(71)*

The single-item global measure of HRQL will be examined as a secondary hypothesis. As for the PCS and MCS scores, the global measure will be analyzed both at a single time point at seven years (t-tests for each comparison) and in longitudinal analyses incorporating all data points.

APPENDIX 19.5 Participating Study Centers and Sites

STATE	Institution Name	City
AK	Providence Alaska	Anchorage
	Fairbanks Mem Hosp	Fairbanks
AL	UAB Div of Prev Med	Birmingham
	Gulf Coast MBCCOP	Mobile
	VAMC Tuscaloosa	Tuscaloosa
AR	Arkansas, Univ of	Little Rock
AZ	Chandler Reg Hosp	Chandler
	Valley Lutheran MC	Mesa
	Greater Phoenix CCOP	Phoenix
	VAMC Phoenix	Phoenix
	Mayo - Scottsdale	Scottsdale
	Sun Health Res Inst	Sun City
	Arizona Cancer Ctr	Tucson
	VAMC So Arizona	Tucson
CA	UCSD - Chula Vista	Chula Vista
	City of Hope Med Ctr	Duarte
	Glendale Mem Hosp	Glendale
	Sierra Nevada Mem	Grass Valley
	San Diego, U of CA	La Jolla
	Loma Linda Univ	Loma Linda
	VAMC Jerry L. Pettis	Loma Linda
	Long Beach Memorial	Long Beach
	VAMC Long Beach	Long Beach
	Los Angeles, U of CA	Los Angeles
	So Calif, U of	Los Angeles
	VAMC Greater LA	Los Angeles
	VANCHCS/EBIRE	Mather
	Northridge Hosp	Northridge
	Bay Area CCOP	Oakland
	Kaiser-Oakland	Oakland
	Irvine, Univ of CA	Orange
	VAMC Palo Alto	Palo Alto
	Huntington Mem Hosp	Pasadena
	Sutter Hlth CRG-East	Sacramento
	Kaiser-San Diego	San Diego
	Mt Zion Cancer Ctr	San Francisco
	VAMC San Francisco	San Francisco
	Santa Clara Valley	San Jose
	Santa Rosa CCOP	Santa Rosa
	Stanford University	Stanford
	Harbor-UCLA	Torrance
	Lionel B. Katchem	Upland
CO	Penrose-St Francis	Colorado Springs
	Colorado Ca Res Prog	Denver
	Colorado, Univ of	Denver
	Rocky Mountain CC	Ft. Collins
	St Mary-Corwin MC	Pueblo

STATE	Institution Name	City
CT	Connecticut, Univ of	Farmington
	New Britain Gen Hosp	New Britain
	Lawrence & Mem Hosp	New London
	Hem/Onc PC	Stanford
DC	DC United MBCCOP	Washington
	George Washington U	Washington
	Providence Hospital	Washington
	Sibley Mem Hosp	Washington
	VAMC Washington DC	Washington
	Walter Reed AMC	Washington
DE	Beebe Hospital	Lewes
	Christiana Care Hlth	Newark
	Nanticoke Mem Hosp	Seaford
FL	Boca Raton Comm Hosp	Boca Raton
	VAMC Gainesville	Gainesville
	Baptist Med Ctr	Jacksonville
	Lakeland Regional CC	Lakeland
	Miami, Univ of	Miami
	Mount Sinai CCOP	Miami Beach
	Florida Community CC	New Port Richey
	Sacred Heart Hosp	Pensacola
	Martin Memorial CC	Stuart
	H Lee Moffitt Cancer	Tampa
	VAMC James A. Haley	Tampa
	Good Samaritan MC	West Palm Beach
GA	Atlanta Reg CCOP	Atlanta
	Midtown Urology PC	Atlanta
	Northside Hospital	Atlanta
	Piedmont Hospital	Atlanta
	Cobb Hosp & Med Ctr	Austell
	DeKalb Medical Ctr	Decatur
	Gwinnett Hosp System	Lawrenceville
	Kennestone Hospital	Marietta
	Southern Reg Med Ctr	Riverdale
	Memorial Medical Ctr	Savannah
	Kaiser Permanente-GA	Tucker
	Val Oak Prof Corp	Valdosta
HI	Hawaii CCOP	Honolulu
IA	Mary Greeley MC	Ames
	Cedar Rapids CCOP	Cedar Rapids
	Genesis Medical Ctr	Davenport
	Iowa Oncology CCOP	Des Moines
	Iowa Hosp, Univ of	Iowa City
	VAMC Iowa City	Iowa City
	Mercy MC-North Iowa	Mason City
	Ottumwa Regional HC	Ottumwa
	Siouxland Hem-Onc	Sioux City

STATE	Institution Name	City
ID	St Alphonsus Reg MC	Boise
	St Luke's/Mt States	Boise
	N Idaho Cancer Ctr	Coeur d'Alene
IL	MacNeal Hospital	Berwyn
	Chicago Consortium	Chicago
	Chicago Hospitals, U	Chicago
	Illinois, Univ of	Chicago
	Mt Sinai Hosp MC	Chicago
	Northwestern Univ	Chicago
	Resurrection Health	Chicago
	Rush Presbyterian	Chicago
	VAMC Lakeside	Chicago
	VAMC Westside	Chicago
	Central IL CCOP	Decatur
	Decatur Mem Hosp	Decatur
	Sherman Hospital	Elgin
	Evanston Hospital	Evanston
	Ingalls Hospital	Harvey
	VAMC Hines	Hines
	Silver Cross Ca Ctr	Joliet
	LaGrange Mem Hosp	LaGrange
	Loyola University	Maywood
	Lutheran Gen Hosp	Park Ridge
	Illinois Oncology	Peoria
	West Suburban Center	River Forest
	Trinity Med Ctr	Rock Island
	SwedishAmerican Hosp	Rockford
	Memorial Medical Ctr	Springfield
	Carle Cancer Center	Urbana
IN	Methodist Hospitals	Gary
	Indiana University	Indianapolis
	Methodist Cancer Ctr	Indianapolis
	Onc Hem Assoc, Inc	Indianapolis
	Oncology Institute	Lafayette
	Northern Indiana CRC	South Bend
	Gerald P. Murphy	West Lafayette
KS	Kansas, Univ of	Kansas City
	VAMC Leavenworth	Leavenworth
	Stormont-Vail Health	Topeka
	VAMC Topeka	Topeka
	Wichita CCOP	Wichita
KY	Our Lady, Bellefonte	Ashland
	Central Baptist Hosp	Lexington
	Kentucky, Univ of	Lexington
	Baptist Hosp East	Louisville
	VAMC Louisville	Louisville

STATE	Institution Name	City
LA	Baton Rouge General	Baton Rouge
	Ochsner Clinic	Baton Rouge
	Our Lady of the Lake	Baton Rouge
	Terrebonne Hosp	Houma
	Louisiana Onc Assoc	Lafayette
	LSU-New Orleans	New Orleans
	Ochsner CCOP	New Orleans
	Tulane University	New Orleans
	LSU-Shreveport	Shreveport
	VAMC Overton Brooks	Shreveport
MA	Beth Israel Deacones	Boston
	Boston Medical Ctr	Boston
	VAMC Boston	Boston
	Lahey Clinic Med Ctr	Burlington
	Berkshire Hem/Onc	Pittsfield
MD	Anne Arundel Med Ctr	Annapolis
	Greater Baltimore MC	Baltimore
	Johns Hopkins Univ	Baltimore
	Maryland, Univ of	Baltimore
	Mem Hosp, Easton	Easton
	Peninsula Reg MC	Salisbury
	St Joseph Med Ctr	Towson
ME	Maine General MC	Waterville
MI	Bixby Oncology Ctr	Adrian
	Michigan CRC CCOP	Ann Arbor
	Michigan, Univ of	Ann Arbor
	Oakwood Hospital	Dearborn
	Henry Ford Hosp	Detroit
	St John Hospital	Detroit
	St John Macomb Hosp	Detroit
	Wayne State/Karmanos	Detroit
	Hurley Medical Ctr	Flint
	Genesys Reg Med Ctr	Grand Blanc
	Grand Rapids CCOP	Grand Rapids
	Kalamazoo CCOP	Kalamazoo
	Breslin Cancer Ctr	Lansing
	Sparrow Health Sys	Lansing
	Marquette Gen Hosp	Marquette
	Monroe Clinic	Monroe
	N Michigan Hosp	Petoskey
	St Joseph Mercy	Pontiac
	William Beau Hosp	Royal Oak
MI	St Mary's Med Ctr	Saginaw
	Providence Hosp	Southfield
	Munson Med Ctr	Traverse City
MN	Duluth CCOP	Duluth
	VAMC Minneapolis	Minneapolis
	Mayo - Rochester	Rochester
	Metro-Minnesota CCOP	St. Louis Park

STATE	Institution Name	City
MO	Associated Urologist	Columbia
	Freeman Hospital	Joplin
	St John's Reg MC	Joplin
	Kansas City CCOP	Kansas City
	VAMC Kansas City	Kansas City
	Phelps County Reg MC	Rolla
	Ozarks CCOP	Springfield
	St John's Reg HC	Springfield
	Missouri Baptist MC	St. Louis
	VAMC St Louis	St. Louis
	Washington Univ	St. Louis
MS	Mid Delta FP	Cleveland
	Mississippi, Univ of	Jackson
	Delta Hlth Center	Mound Bayou
MT	Montana CCOP	Billings
	Benefis Health Care	Great Falls
NC	Mission St. Joseph's	Asheville
	VAMC Asheville	Asheville
	Presbyterian Hosp	Charlotte
	VAMC Durham	Durham
	Gaston Memorial Hosp	Gastonia
	Wayne Memorial Hosp	Goldsboro
	Margaret R. Pardee	Hendersonville
	Raleigh Hem/Onc	Raleigh
	VAMC Salisbury	Salisbury
	Forsyth Mem Hosp	Winston-Salem
	Southeast CCC CCOP	Winston-Salem
	Wake Forest Univ	Winston-Salem
ND	MeritCare Hosp CCOP	Fargo
	VAMC Fargo	Fargo
NE	Good Samaritan HS	Kearney
	Cancer Resource Ctr	Lincoln
	Alegent Bergan Mercy	Omaha
	Alegent Immanuel Med	Omaha
	Methodist Cancer Ctr	Omaha
NE	Midwest Urol Assoc	Omaha
	Missouri Valley CCOP	Omaha
	Nebraska, Univ of	Omaha
	VAMC Omaha	Omaha
NH	Dartmouth Hitchcock	Lebanon
NJ	Med Ctr of Ocean Cty Brick	
	VAMC New Jersey	East Orange
	Trinitas Hospital	Elizabeth
	Hunterdon Med Ctr	Flemington
	Northern NJ CCOP	Hackensack
	Virtua West Jersey	Marlton
	Mem Hosp, Burlington	Mount Holly
	UMDNJ-New Jersey MS	Newark
	Valley Hospital	Paramus

STATE	Institution Name	City
NJ	Warren Hospital	Phillipsburg
	Atlantic City MC	Pomona
	Riverview Med Ctr	Red Bank
	Mem Hosp of Salem Co	Salem
	Shore Mem Hosp	Somers Point
	Somerset Med Ctr	Somerville
	Community Med Ctr	Toms River
	Capital Health Sys	Trenton
	St Francis Med Ctr	Trenton
	Cooper Med Ctr	Voorhees
NM	New Mexico, Univ of	Albuquerque
NV	Southern Nevada CCOP	Las Vegas
	Washoe Medical Ctr	Reno
NY	VAMC Stratton	Albany
	VAMC Bath	Bath
	Montefiore Med Ctr	Bronx
	Downstate Med Ctr	Brooklyn
	NY Methodist Hosp	Brooklyn
	Roswell Park	Buffalo
	VAMC Western NY	Buffalo
	WNY Urology Assoc	Buffalo
	Bassett Research Ins	Cooperstown
	Glens Falls Hospital	Glens Falls
	Queens Hospital Ctr	Jamaica
	North Shore CCOP	Manhasset
	Columbia University	New York
	VAMC Northport	Northport
	Nyack Hospital	Nyack
	Rochester, Univ of	Rochester
	SUNY Stony Brook	Stony Brook
	Syracuse CCOP	Syracuse
	VAMC Syracuse	Syracuse
	Faxton-St Luke's	Utica
	Dickstein CTC	White Plains
OH	Summa Health System	Akron
	Aultman Hospital	Canton
	Mercy Medical Center	Canton
	Cincinnati, Univ of	Cincinnati
	Good Samaritan Hosp	Cincinnati
	Cleveland Clinic	Cleveland
	Ireland Cancer Ctr	Cleveland
	VAMC Cleveland	Cleveland
	Columbus CCOP	Columbus
	Ohio State Univ	Columbus
	Dayton CCOP	Dayton
	Fremont Mem Hosp	Fremont
	Lima Memorial Hosp	Lima
	NW Ohio Oncology Ctr	Maumee
	St Charles Hospital	Oregon
	Firelands Comm Hosp	Sandusky
	Flower Hospital	Sylvania
	Medical College-Ohio	Toledo
	St Vincent Med Ctr	Toledo

STATE	Institution Name	City
OH	Toledo CCOP	Toledo
	Toledo Clinic	Toledo
	Toledo Hospital	Toledo
	Fulton County HC	Wauseon
OK	Comanche Co Mem Hosp	Lawton
	Muskogee Reg Med Ctr	Muskogee
	INTEGRIS Oncology	Oklahoma City
	Mercy Health Center	Oklahoma City
	Oklahoma, Univ of	Oklahoma City
	VAMC Oklahoma City	Oklahoma City
	St Francis Hospital	Tulsa
	St John Med Ctr	Tulsa
OR	St Charles Med Ctr	Bend
	Willamette Valley	Eugene
	Columbia River CCOP	Portland
	Kaiser Permanente	Portland
	Oregon Hlth Sci Univ	Portland
PA	Abington Mem Hosp	Abington
	Lehigh Valley Hosp	Allentown
	Sacred Heart Hosp	Allentown
	St Luke's Hospital	Bethlehem
	Bryn Mawr Hospital	Bryn Mawr
	Geisinger Clinic	Danville
	Mercy Catholic MC	Darby
	Doylestown Hospital	Doylestown
	Delaware Co Mem Hosp	Drexel Hill
	Easton Hospital	Easton
	Regional Cancer Ctr	Erie
	Pinnacle Hlth Sys	Harrisburg
	Hershey Med Ctr	Hershey
	Conemaugh Mem Hosp	Johnstown
	Lancaster Gen Hosp	Lancaster
	St Mary Hospital	Langhorne
	Central Montgomery	Lansdale
	VAMC Lebanon	Lebanon
	Central PA Hem & Med	Lemoyne
	Riddle Memorial Hosp	Media
	Norristown Reg CC	Norristown
	Paoli Memorial Hosp	Paoli
	Chestnut Hill HC	Philadelphia
	Eastwick Primary	Philadelphia
	Fox Chase Cancer Ctr	Philadelphia
	Kimmel Cancer Ctr	Philadelphia
	Pennsylvania Hosp	Philadelphia
	Pennsylvania/Univ of	Philadelphia
	Phoenixville Hosp	Phoenixville
	Pittsburgh Ca Inst	Pittsburgh
	VAMC Pittsburgh	Pittsburgh
	Pottstown Memorial	Pottstown
	Reading Hosp & MC	Reading
	St Joseph Med Ctr	Reading
	Grand View Hospital	Sellersville

STATE	Institution Name	City
PA	Chester County Hosp	West Chester
	S Chester Cty MC	West Grove
	Main Line/Lankenau	Wynnewood
	York Cancer Center	York
PR	Andres Grillasca	Ponce
	Altamira Family Med	San Juan
	Centro Clinico	San Juan
	Gonzalez Martinez	San Juan
	Miguel Sosa Padilla	San Juan
	San Juan MBCCOP	San Juan
	VAMC San Juan	San Juan
RI	VAMC Providence	Providence
SC	Anderson Area MC	Anderson
	Roper Hospital Inc	Charleston
	Palmetto Richland MH	Columbia
	McLeod Reg Med Ctr	Florence
	Greenville CCOP	Greenville
	Upstate Carolina	Spartanburg
SD	Sioux Community CC	Sioux Falls
TN	East Tennessee State	Johnson City
	VAMC James A Quillen	Johnson City
	Holston Valley Hosp	Kingsport
	Knoxville, U of TN	Knoxville
	Thompson Ca Surv Ctr	Knoxville
	Baptist Mem Hosp	Memphis
	Memphis, U of TN	Memphis
	VAMC Memphis	Memphis
	Meharry Med College	Nashville
	Vanderbilt Univ	Nashville
	Methodist Reg CC	Oak Ridge
TX	Texas Oncology, PA	Abilene
	Harrington/TexasTech	Amarillo
	Baylor Univ Med Ctr	Dallas
	Methodist, Dallas	Dallas
	Presbyterian Hosp	Dallas
	US Oncology	Dallas
	UT Southwestern	Dallas
	VAMC Dallas	Dallas
	El Paso CTC	El Paso
	Harris Methodist	Fort Worth
	Galveston, U of TX	Galveston
	UTMB-Family Med	Galveston
	Baylor College	Houston
	MD Anderson	Houston
	VAMC Houston	Houston
	Wilford Hall Med Ctr	Lackland AFB
	Texas Tech Univ	Lubbock
	San Antonio, U of TX	San Antonio
	Scott & White CCOP	Temple

STATE	Institution Name	City
TX	VAMC Central Texas	Temple
	Beeler-Manske Clinic	Texas City
	Tyler Cancer Center	Tyler
	Tyler, U of TX	Tyler
	Waco Cancer Care	Waco
UT	LDS Hospital	Salt Lake City
VA	Danville Reg Med Ctr	Danville
	Inova Fairfax CGOP	Falls Church
	Sentara Cancer Inst	Norfolk
	Med Col of Virginia	Richmond
	VAMC McGuire	Richmond
VT	Green Mountain	Bennington
	Vermont Cancer Ctr	Burlington
WA	Cascadia Clin Trials	Bellingham
	Puget Sound Ca Ctr	Edmonds
	Northwest Hosp	Seattle
	Swedish Medical Ctr	Seattle
	VAMC Puget Sound	Seattle
	Virginia Mason CCOP	Seattle
	Cancer Care NW	Spokane
	Sacred Heart Med Ctr	Spokane
	Northwest CCOP	Tacoma
WI	Wisconsin, Univ of	Madison
	Marshfield Clinic	Marshfield
	Med Col of Wisconsin	Milwaukee
	Sinai Samaritan MC	Milwaukee
	Reg CC-Oconomowoc	Oconomowoc
	Regional CC-Waukesha	Waukesha
	Wausau Hospital	Wausau
WV	Camcare Health	Charleston
	WVU-Morgantown	Morgantown
	Schiffler Cancer Ctr	Wheeling
AB	Prostate Cancer Inst	Calgary
BC	Vancouver Hospital	Vancouver
	Capital Region PC	Victoria
NS	Queen Elizabeth HSC	Halifax
ON	Hamilton Reg Ca Ctr	Hamilton
	London HSC	London
	London Reg Ca Ctr	London
	Ottawa General Hosp	Ottawa
	Northwestern Ontario	Thunder Bay
	Princess Margaret	Toronto
	Sunnybrook & Women's	Toronto
PR	Orocovis Med Ctr	Orocovis
QC	McGill University HC	Montreal
	Centre de Recherche	Quebec
	Sherbrooke Univ Hosp	Sherbrooke

Appendix 19.6 Model Informed Consent - Collection and Storage of Additional Blood Specimens

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 that 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 asked to provide informed consent.

Readability Statistics:		
Flesch Reading Ease	57.6	(targeted above 55)
Flesch-Kincaid Grade Level	9.1	(targeted below 8.5)

S0000, "SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL (SELECT)" COLLECTION AND STORAGE OF ADDITIONAL BLOOD SPECIMENS

You are taking part in SELECT. SELECT is a clinical trial (a type of research study) testing whether vitamin E and selenium can prevent prostate cancer. SELECT is also looking at whether other factors, for example genes and hormones, affect risk of prostate cancer. The blood sample(s) you have already given will help us in this research.

WHY IS THIS STUDY BEING DONE?

We are now asking for your consent to give another blood sample. We want to be able to better answer questions about how to prevent prostate cancer and other diseases that occur in men your age. We also would like to collect more blood samples for future research.

There are many important questions that can only be answered using blood collected during the SELECT study. For example, we hope to find factors that predict who will benefit the most from the SELECT supplements. We also hope to learn more about the biology of how the SELECT supplements work to prevent disease.

WHAT IS INVOLVED IN THE STUDY?

If you agree to provide another blood sample, we will collect about 18 ml (about 4 teaspoons) of blood. Your blood will be sent to the Southwest Oncology Group research storage lab, where it will be stored. Your blood will be used to see whether inherited factors or compounds found in blood are related to cancer. With your permission, your blood may also be stored and used for future research. If needed, scientists will also use information about your health, such as your age, weight and health conditions, in their research.

WHAT ARE THE RISKS OF THE STUDY?

There are no likely risks from giving another blood draw. You will have the discomfort of another needle stick. There is a remote risk that information from your blood sample could become known to a health insurer or employer. This information could affect your application for insurance or employment. However, as explained in "What about Confidentiality?" no identifying information (name, birth date, phone number, address) is on your blood sample. It is not likely that any of your research results could be linked to you or your family. The Southwest Oncology Group is responsible to assure that all information about you and your blood sample remains private.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We cannot and do not guarantee you will benefit directly if you take part in this additional blood draw. There are no personal benefits from taking part in this extra blood draw. Results from these tests on your blood cannot be used for your medical care. Therefore, the results of these tests will not be given to you or your doctor. However, we hope the information learned from this study will add to our understanding of prostate cancer prevention and treatment, and may help improve the health of future generations

WHAT ABOUT CONFIDENTIALITY?

Scientists studying the blood will not have any identifying information such as name or address. These scientists will use the SELECT unique ID numbers to identify the information for each man in the study.

The SELECT trial will make every effort to keep your personal information private.

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; the makers of the vitamin E, selenium and placebo pills for the study, 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 COSTS?

There are no costs to take part in this study, beyond the extra time to complete the blood draw at a regular SELECT visit. In the highly unlikely event of injury or illness resulting from this study, medical treatment will be provided at usual charge. No funds have been set aside to compensate you in the event of injury. You will receive no payment for taking part in the study. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this extra blood draw is up to you. You may choose not to take part and you may leave the study at any time. Leaving the study will not result in any penalty or any effect on your participation in SELECT. However, if you decide to withdraw from the study, we ask you to talk to the study doctor and your regular doctor first.

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*.

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 site…
www/cancer.gov

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

If you agree to allow your blood samples to be sent in, they will be used for future research in the manner you approved for use of your samples in the consent form you previously signed for the SELECT study.

If you decide to take your samples out of a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the Southwest Oncology Group Operations Office. Please state in the written withdrawal whether you would prefer to have the samples destroyed or returned to the study doctor.

SIGNATURE

You are deciding whether or not to take part in an additional blood draw and submission for SELECT. If you sign this, you are giving permission that your samples may be kept for use in research related to your participation in the SELECT trial. 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. Feel free to ask any questions you have about the study before signing.

Your consent to participate in SELECT was given in a separate form.

Participant _____Date _____

19.7 Informed Consent – Centralized Extension of Follow-Up

This informed consent form has been reviewed by the DCP/NCI and is the official consent document for this study. Editorial changes to this document 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 asked to provide informed consent.

Readability Statistics:	
Flesch Reading Ease	57.2 (targeted above 55)
Flesch-Kincaid Grade Level	9 (targeted below 8.5)

S0000, "SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL (SELECT)" CENTRALIZED EXTENSION OF FOLLOW-UP

This form is to tell you about the SELECT Centralized Extension of Follow-up. You are being invited to participate in this study because you are part of SELECT. SELECT tested whether vitamin E and selenium can prevent prostate cancer and found no benefit from either study supplement. After a final visit at your SELECT study site, you will no longer be seen in person by the SELECT study staff.

You are being asked to extend your participation in SELECT for about 2 to 5 years. You are also being asked to consent to centralized follow-up instead of local follow-up. The SELECT Coordinating Center will perform all of the centralized follow-up. The SELECT Coordinating Center is part of the Southwest Oncology Group and is located at Cancer Research and Biostatistics in Seattle, Washington. This follow-up study will be offered to all men currently participating in SELECT.

WHY IS THIS STUDY BEING DONE?

We would like to know whether taking vitamin E or selenium for several years has any effect on men's health in the future. We want to continue to answer questions about how to prevent prostate cancer. We also want to learn more about other diseases that occur in men your age.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

This study will be offered to all men currently participating in SELECT. We expect up to 24,000 men in the United States, Canada and Puerto Rico to join.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH?

If you agree, your study site will release your current personal contact information to the SELECT Coordinating Center. You are also being asked to allow us to contact your spouse, close relative, or friend if we cannot locate you. If you move, and we are not able to find you, we may try to locate you through nationally available records. The SELECT Coordinating Center will use your contact information to send you a questionnaire about once a year in the month of your birthday. This questionnaire will be sent through the mail. Questionnaires will be available in English or Spanish.

This questionnaire will ask questions about your health. We may ask about prostate cancer, other cancers, diabetes, Alzheimer's disease, eye diseases or other health issues. The questionnaire may be modified in the future. We estimate that the questionnaire will take no more than thirty (30) minutes to complete. Additional questionnaires could be added in the future. Your participation in completing these would be up to you.

You may complete the questionnaire on paper and then mail it back to us. We will pay postage. If you wish, you may enter the information on a secure website instead of mailing the questionnaire to us. If you are unable to respond by mail or to complete the questionnaire on a website, we may need to contact you by telephone.

If we receive your questionnaire by mail, we will scan it into our computer system. After we are sure that the data have been entered correctly, we will shred the original questionnaire. If you fill out your questionnaire on our secure website, your answers will be saved directly into our computer system.

Your answers will be reviewed by trained staff. If we need more details, we will send you a medical release in the mail to sign and return to us. A medical release lets us contact your doctor to get more information. We will send these if we need to know more about cancer or another serious health problem. If you report a diagnosis of prostate cancer, we will send your signed medical release to Dr. Scott Lucia at the SELECT Pathology Review Laboratory located at the University of Colorado. Dr. Lucia will request a pathology report and specimens. If you report a diagnosis of another type of cancer, we will send the signed medical release to your doctor and ask your doctor for the medical records we need to confirm the diagnosis. If you report an eye disease, we will send your signed medical release to Dr. William Christen at Brigham and Women's Hospital. Dr. Christen will request the medical records to confirm the diagnosis. If you report a colorectal screening procedure, we will send your signed medical release to Dr. Peter Lance at Arizona Cancer Center. Dr. Lance will request the pathology report and specimens.

If we do not receive your completed questionnaire, we will remind you. This reminder may be by telephone, mail, or e-mail.

If there is urgent information we feel may affect your participation, we will send it to you.

We will also send periodic newsletters and other study information.

HOW LONG WILL I BE IN THE STUDY?

We do not yet know the length of this study, but we project it to be two to five years.

CAN I STOP BEING IN THE STUDY?

Yes. You can choose to stop at any time by notifying the SELECT Coordinating Center. If you leave the SELECT extension study, it will not affect your personal medical care or your medical insurance coverage. If you decide to take your samples out of a Southwest Oncology Group Specimen Repository in the future, send a written withdrawal of consent to the SELECT Coordinating Center.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

The primary risk from providing your contact information and agreeing to continue with centralized contact from the SELECT study is the possible leak of personal health information and contact information due to the mailing of information (either by regular mail or by computer). Although the Southwest Oncology Group is responsible to assure that all information that we receive about you remains private, we cannot guarantee that written information in the questionnaires may not be seen during the mailing or web entry process.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There are no personal benefits from taking part in this centralized contact. The information that you report to SELECT, and information that we collect from your medical records will be reviewed, but the results of the review will not be shared with you or your doctor. However, we hope the information learned from this study will add to our understanding of prostate cancer. We also hope that this information will help our understanding of other diseases in men your age. This information may help improve the health of future generations.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose not to participate in this extension, and to end your participation in SELECT now.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If we publish the information we learn from this study in a medical journal or present it at a scientific meeting, you will not be identified by name or in any other way.

Data are stored in a secure database at the SELECT Coordinating Center, and our staff has been trained to protect your privacy. Only the staff at the SELECT Coordinating Center will have access to your information for the purpose of mailings and maintaining and updating your study records.

If you choose to send your questionnaire through the mail, it is possible that others may see your answers or personal information if the envelope is lost or not sealed properly. If you choose to submit your questionnaire on our secure website, it is possible that others may see your answers or personal information if the computer you use is not secure.

If you are asked to sign a medical release, this release will be used to contact your personal doctor for more information about a specific health issue. Information on the medical release will be kept confidential. We will also keep any information we receive from your doctor confidential.

Other organizations may request access to our data. This would be done for quality assurance and data analysis. Your name and personal information will not be shared with these organizations unless required by law. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- the Southwest Oncology Group (including Cancer Research and Biostatistics)
- public health agencies and other government agencies (including non-U.S.) as authorized or required by law - e.g. The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- other people or organizations assisting with Southwest Oncology Group research efforts
- central laboratories, central review centers, and central reviewers. The central laboratories and review agencies may also give your health information to those groups listed above.
- the makers of the vitamin E, selenium and placebo pills used in this study

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There are no costs to take part in this study, beyond the time and effort to complete the annual questionnaires. Medical treatment is not provided by the study. No funds have been set aside to compensate you in the event of problems that might occur during the course of this study. You will not be paid for being in the study. This study does not replace your usual medical care.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this centralized contact and release of medical records is up to you. You may choose not to take part and you may leave the study at any time. Leaving the study will not result in any penalty.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

For questions about the study or a research-related injury, contact the researcher Dr. John Crowley, Principal Investigator, SELECT Coordinating Center at 206/652-1338.

For questions about your rights as a research participant, contact the Cancer Research and Biostatistics Institutional Review Board (which is a group of people who review the research to protect your rights) at 206/342-1692.

WHERE CAN I GET MORE INFORMATION?

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 site…
www.cancer.gov

Visit the SELECT web site..
www.crab.org/select

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

Investigator's statement

This statement is made by Dr. John Crowley, the Principal Investigator for the SELECT Coordinating Center:

I have provided the explanation of the SELECT extension study that is in this form. I have designated the person you are seeing today at your study site to present this consent form to you. This person will ensure that you had an opportunity to discuss the procedures (including risks) and to ask any questions. My designee will give you a signed and dated copy of the consent form.

_____ _____
Signature of Designee at Study Site Date

Willingness to participate in additional substudies

You may be asked to participate in special substudies which will require completing additional questions.

I agree to be contacted with information about special substudies.

|_| Yes |_| No Initials: _____

SIGNATURE

You are deciding whether or not to provide your contact information to take part in a centralized extension of follow-up for SELECT. If you sign this, you are agreeing to be contacted once a year by mail. You may be contacted by phone or email. You are agreeing to complete an annual questionnaire about your health. If you sign, it means that you have decided to volunteer to take part in this study. If you do not sign this, your participation in SELECT will end.

I have been given a copy of all 6 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

PARTICIPANT _____

DATE _____

All three signature/initial items must be placed on the last page of the consent form as that is the only page being sent to the Coordinating Center.]

[Study site must put standard identifiers (site #, ppt #, ppt initials) at the bottom of the signature page before faxing the page to the SELECT Coordinating Center.]

19.8 Alternatives for Transition to Centralized Follow-Up (Plans B and C)

Based on Study Site feedback that some local Institutional Review Boards disapproved procedures for centralization of follow-up as presented in Amendment #5, the SELECT Statistical Center offers the two alternatives for centralization as listed below. These options are only for sites that are unable to get Amendment #5 approved and are not intended as a substitute for those Study Sites that received approval. Consultation with the SELECT Statistical Center is required before any site may implement these alternative plans.

Plan B Summary –

The Study Site describes centralized follow-up to the participant as outlined in Section 7.13 of the protocol but does not obtain informed consent. Instead, the Study Site requests that the participant complete a Release of Information giving the Study Site permission to obtain enough information on Form 701-"Participant Contact Information for Centralized Follow-Up" so that the SELECT Coordinating Center can contact the participant. Form 701 will be submitted to the SELECT Coordinating Center, which will then contact the participant by mail using a standard cover letter, accompanied by a Checklist and an Information Sheet. The letter instructs him to read the CRAB/SELECT Coordinating Center consent form and sign and return the Signature Page of the consent form. Once the Coordinating Center receives the signed Signature Page, the participant will be registered to centralized follow-up.

Plan C Summary –

The Study Site provides the participant with an Information Sheet describing the SELECT Coordinating Center and centralized follow-up, and asks the participant to contact the Coordinating Center if he is interested in participating. If the participant contacts the SELECT Coordinating Center and agrees to provide his contact information, the participant, the Coordinating Center will then contact the participant by mail and request informed consent as indicated above under Plan B.

All of the materials necessary to implement Plan B or Plan C may be found on the Workbench by accessing the Study Transition button or in Section 4.7 of the Study Manual.