



**Southwest
Oncology Group**

A National Clinical Research Group

September 3, 2002

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

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

RE: **S0000A**, "Prevention of Alzheimer's Disease With Vitamin E and Selenium (PREADVISE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Markesbery, et al.

REVISION #1

Study Coordinator: William Markesbery, M.D.

Phone number: 859/323-6040

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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

The study referenced above has been revised to allow more flexibility for registration to PREADVISE in conjunction with SELECT randomization. Sections 5.1 (page 6), Section 7.2 (page 7) and Section 9.0 (page 9) have been revised to reflect the following:

"Participants who were randomized to SELECT prior to October 1, 2002 may be registered to PREADVISE: 1) at, or within 28 days following their first Six Month SELECT Visit, or 2) at, or within 28 days following their first Annual SELECT Visit. Participants who are randomized to SELECT on or after October 1, 2002, may be registered to PREADVISE only at, or within 28 days following their SELECT randomization."

Sections 5.3 (page 6) and 7.2 (page 7) were revised to indicate that the applicable age requirement is "at this time of registration to PREADVISE" rather than "at the time of SELECT randomization".

Operations Office

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

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Replacement pages are enclosed for pages 6, 7 and 9. Please insert them into 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
 Cecil Runyons - PREADVISE



Southwest Oncology Group

A National Clinical Research Group

April 29, 2002

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

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

RE: **S0000A**, "Prevention of Alzheimer's Disease With Vitamin E and Selenium (PREADVISE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Markesbery, et al.

STATUS NOTICE

Study Coordinator: William Markesbery, M.D.

Phone number: 859/323-6040

E-mail: wmarkesbery@aging.coa.uky.edu

IRB Review Requirements

(√) Full board review required. Reason:

(√) Initial activation (should your institution choose to participate)

() Increased risk to patient

() Complete study redesign

() Addition of tissue banking requirements

() Study closure not built into study design

() Expedited review allowed

() No review required

ACTIVATION

The study referenced above will be officially activated for participant recruitment effective May 17, 2002.

If your institution intends to participate in this study, please obtain local IRB approval, document on the enclosed IRB Certification Form and forward a copy to the Operations Office by FAX at 210/677-0006.

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.
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NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance
Cecil Runyons - PREADVISE

Operations Office

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135 **UNIVERSITY OF KENTUCKY AND SOUTHWEST ONCOLOGY GROUP**

136 PREVENTION OF ALZHEIMER'S DISEASE WITH VITAMIN E AND SELENIUM (PREADVISE)

137 PHASE III ANCILLARY TO **S0000** - SELECT

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159 PARTICIPANTS: See Appendix Section 19.5 in main SELECT study (**S0000**)

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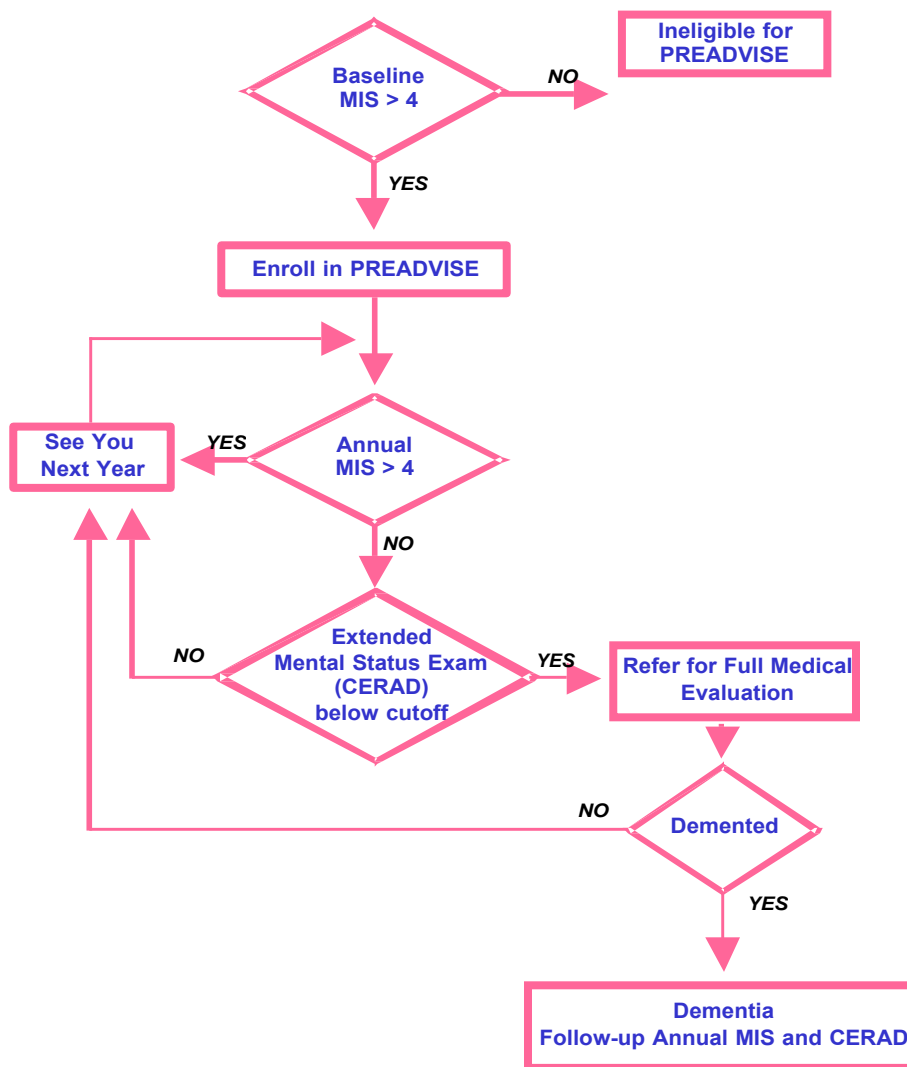
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1.0 OBJECTIVES

- 1.1 Primary Objective - To define the effect of selenium and vitamin E in combination in the reduction of the incidence of Alzheimer's disease (AD), as determined by mental status screening and clinical evaluation, in a population of men age 62 or older (60 if of African descent or Hispanic) participating in SELECT.
- 1.2 Secondary Objectives
 - a. To define the effect of selenium and vitamin E alone in the reduction of the incidence of Alzheimer's disease (AD), as determined by mental status screening and clinical evaluation, in a population of men age 62 or older (60 if of African descent or Hispanic) participating in SELECT.
 - b. To assess the combined and individual effects of selenium and vitamin E in the reduction of the incidence of other neurodegenerative diseases, including dementia with Lewy bodies, frontotemporal dementia (including Pick's disease), corticobasal degeneration, progressive supranuclear palsy, and vascular dementia.
 - c. Evaluate the sensitivity and specificity of the Memory Impairment Screen (MIS) relative to the Consortium to Establish a Registry in AD (CERAD) mental status measures (in a subsample of 500 participants).
 - d. Study the features of normal cognitive aging (in a subsample of 200 participants) and to assess the effect of selenium and vitamin E on this process.
 - e. Study the progression of AD and other neurodegenerative diseases in participants clinically diagnosed with AD or other dementia.
- 1.3 Tertiary Objective - To evaluate the association of apolipoprotein E (APOE) ϵ alleles and other potential biological molecular markers with the risk of Alzheimer's disease and other neurodegenerative diseases in this population.

2.0 BACKGROUND

Past findings: Normal aging is often accompanied by changes in physical and mental health. However, pathological aging involves a host of disorders. The most common, Alzheimer's disease (AD), currently afflicts roughly 4 to 6 million persons in the United States. It is estimated that up to 22 million persons will develop AD in the United States by the year 2025 if effective treatment or prevention are not found. Additionally, there will be an estimated 2 to 4 million related dementias such as dementia with Lewy bodies, frontotemporal dementia, and vascular dementia.

For this study, age-associated changes in memory will be monitored as a "sentinel system" for the development of dementia. These data are needed to better understand the incidence and prevalence of dementia over the age of 62 and how it may be influenced by antioxidant supplements. Current estimates from Caucasian populations suggest that roughly 11% of persons over the age of 65 have AD. However, epidemiological data show only a modest incidence for AD in Caucasian men aged 55 to 64 implying that it would not be cost effective to screen men younger than age 62 for AD. These same data show that AD incidence quickly rises in men after age 64. Some studies suggest that Hispanic groups and people of African descent may have a higher AD incidence estimated at 2 to 4 times that of Caucasian groups. Further, as dementia prevalence increases with age, some estimates for AD in persons over the age of 80 are as high as 48%.

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257 The primary neuropathological changes in the AD brain involve cell loss, accumulation of
258 neurofibrillary tangles and senile plaques as well as the loss of neurotransmitters. Current therapy
259 with anticholinesterase compounds (e.g., Aricept, Exelon, Reminyl, Cognex) and antioxidants
260 (vitamin E) have provided modest symptomatic relief over the short term, at best. Therefore,
261 prevention strategies may prove to be the most cost effective method for reducing the burden
262 associated with dementia. Based on in vitro and in vivo studies, there is a good rationale for using
263 antioxidant treatments in an effort to impede the development of dementia.

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265 Over the past decade, genetic risk factors associated with AD have implicated chromosomes 14,
266 19, and 21 in familial AD. Research has shown that a small percentage of AD patients (< 2%),
267 generally with presenile onset, have clear autosomal dominant inheritance. These families have
268 shown linkage to mutations in the amyloid precursor protein (APP) on chromosome 21, or to an
269 unidentified gene on chromosome 14. Several papers have shown that patients with "sporadic"
270 or nonfamilial AD seem to have a linkage to chromosome 19 through the ApoE alleles. (20) Data
271 show that the ApoE ϵ/ϵ allele is over-represented in AD relative to elderly control subjects. (23)
272 These data also suggest a gradient of risk such that persons with the ApoE ϵ/ϵ genotype may
273 develop AD at a significantly earlier age than ApoE ϵ/δ heterozygotes, who in turn may develop
274 dementia earlier than ApoE δ/δ homozygotes. These data suggest that the ApoE ϵ allele is
275 an important risk factor that may account for about 40% of nonfamilial AD cases. The addition of
276 the tertiary aim for this study provides the PREADVISE investigators the opportunity to evaluate
277 not only APOE but other unknown, yet to be defined molecular markers that may be associated
278 with AD or other dementia. Thus circumventing the need to amend the protocol in the future for
279 the purposes of examining associations between molecular markers and AD. The sample for the
280 ApoE genotype testing will come from stored blood specimens at the SELECT Biospecimen
281 Storage Facility at NCI-Frederick, located in Frederick, MD.

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283 Since men who are at risk for prostate cancer are also over the age of 50, this study represents a
284 unique opportunity to assess the impact of the SELECT prevention strategy on the evolution of
285 dementia, especially as the incidence and prevalence of dementia rises with age.

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287 **Oxidative Stress in Alzheimer's Disease:** At present, no effective therapies are available
288 for AD and it is highly desirable to develop preventive measures. Although the etiologies of AD
289 are not known, a partial understanding of the cascade of pathophysiologic events involved in
290 neuron degeneration has been achieved, some of which may have modifiable steps. Oxidative
291 stress plays a major role in the pathogenesis of neuron degeneration in AD and probably other
292 neurodegenerative diseases. Most investigators believe that prevention is the key to AD and that
293 preventive measures should start early in life. A growing body of evidence indicates that
294 increased oxidative stress, from free radical damage to cellular functions, is associated with
295 neurodegenerative diseases. The evidence has been most clearly demonstrated for AD, where
296 multiple studies show increased oxidation of brain lipids, proteins, carbohydrates and DNA.

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298 Enhancement of brain levels of selenium (Se) might increase antioxidant defense mechanisms in
299 AD by increasing brain glutathione peroxidase and glutathione concentrations and thioredoxin
300 reductase levels. Increasing Se levels might also enhance the relationship between Se and
301 vitamin E. The possibility exists that together they can be much more efficient as antioxidants.
302 Organized trials of Se alone or in conjunction with vitamin E in individuals at risk for AD have not
303 been carried out previously.

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305 A double-blind, placebo-controlled, randomized multicenter trial of vitamin E and selegiline in 341
306 AD patients of moderate severity for two years revealed mild slowing of the progression of the
307 disease in both groups. Vitamin E was superior to selegiline or combination therapy in delaying
308 the time to the primary outcome (death, institutionalization, loss of ability to perform activities of
309 daily living or severe dementia). (22) Importantly, no significant side effects were encountered in
310 the dose of 2,000 units of vitamin E daily. A similar large trial of 2,000 IU of vitamin E daily in

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312 Parkinson's with dementia patients revealed no improvement, but also showed no significant side
313 effects. (15) Although the AD study showed that vitamin E slowed the progression of the
314 disease slightly when given over a two-year period, additional studies are needed to establish the
315 value of lower doses of vitamin E in the long-term management of AD.

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317 In summary, it appears that the key to AD is prevention and that preventive measures should start
318 early in life. There are compelling data that the brain in AD is under heightened oxidative stress.
319 The PREADVISE study is aimed at reducing oxidative stress using antioxidant agents in the
320 presymptomatic stage to delay or prevent the onset of the disease.

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322 Inclusion of Minorities and Underserved/Uninsured

323 It is a standing policy of the Southwest Oncology Group to include eligible patients and/or
324 participants of both sexes and all races and ethnicities in all Group clinical trials, except as
325 restricted by specific disease site (e.g., prostate, gynecological). The proposed participant
326 population for the full SELECT study (**S0000**) will consist of males, due to the specific disease
327 site (prostate), and will include minority populations, including, but not limited to, African-
328 Americans, Hispanics, Asian-Americans, as well as medically underserved populations. As
329 African-American males are at higher risk for the development of prostate cancer, an attempt will
330 be made to over-recruit this population through specific recruitment and adherence strategies.
331 Previous minority accrual in Southwest Oncology Group genitourinary and cancer control studies
332 in 1998 and other relevant studies is shown below:
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ACCRUAL	Total	White	Black	Hispanic	Other
<u>Committee (1998)</u>					
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%)
<hr/>					
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%)
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335 **3.0 DRUG INFORMATION**

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337 Drug information is not applicable to this study. This study will use the same agents as the main
338 SELECT protocol (**S0000**).

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341 **4.0 STAGING CRITERIA**

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343 Staging Criteria are included in Appendix 19.2 of the main SELECT protocol (**S0000**) as a
344 reference for staging participants who develop prostate cancer.

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347 **5.0 ELIGIBILITY CRITERIA**

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SELECT Participant No. _____

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

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5.1 The potential PREADVISE participant must be a SELECT participant. Participants who were randomized to SELECT prior to October 1, 2002 may be registered to PREADVISE: 1) at, or within 28 days following their first Six Month SELECT Visit, or 2) at, or within 28 days following their first Annual SELECT Visit. Participants who are randomized to SELECT on or after October 1, 2002, may be registered to PREADVISE only at, or within 28 days following their SELECT randomization. Follow-up for PREADVISE will be at each subsequent Annual SELECT Visit.

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5.2 A baseline Memory Impairment Screen (MIS) must be administered prior (within 30 days) to enrollment in PREADVISE and the participant must score greater than 4. Participants whose scores are 4 or less will not be registered to PREADVISE.

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5.3 Participants must be age 62 or older at the time of registration to PREADVISE. Men of African or Hispanic descent must be 60 or older at the time of registration to PREADVISE.

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5.4 The participant must not have any of the following neurological conditions based on self-report (were told by a physician):

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Alzheimer's disease, or any other form of dementia such as Pick's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, significant cognitive and motor impairment from a stroke or corticobasal degeneration.

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Huntington's disease, epilepsy, Parkinson's disease, brain tumor, multiple sclerosis, manic-depressive disorder, or schizophrenia.

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5.5 The participant must not have had a head injury with prolonged loss of consciousness (over 30 minutes) within the past five years.

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5.6 The participant must not have had an alcohol or substance abuse diagnosis in the past 24 months.

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5.7 The participant must not have had a diagnosis of depression or anxiety disorder in the past 4 months.

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5.8 The participant must not currently use of any of the following medications: Aricept, Cognex, Exelon, Reminyl, or Hydergine.

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5.9 The participant must not have blindness, deafness, language difficulties or any other disability that may prevent completion of the MIS.

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5.10 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 before PREADVISE procedures are initiated.

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5.11 At the time of participant registration, the treating institution's name and ID number must be provided to the Statistical Center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

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6.0 STRATIFICATION FACTORS

Stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

All participants will receive treatment as outlined in **S0000**.

Please refer all questions regarding the Memory Impairment Screen (MIS) or any procedures related to PREADVISE to Dr. William Markesbery or the PREADVISE staff at 866/846-1412.

Detailed procedures for the Baseline Visit and Annual Visits can be found in the PREADVISE Study Manual which is Appendix J of the SELECT Study Manual.

7.1 The MIS is a brief memory screening test that can easily be administered by the Study Site staff at the participating sites. Training for administering the MIS will be conducted through workshops during the semi-annual Southwest Oncology Group Meetings. Detailed instructions can also be found in the PREADVISE Study Manual. The scoring of the MIS (0-8) will be completed by the Study Site staff. The time required to administer the MIS is 5 to 10 minutes.

7.2 Registration Visit

PREADVISE registration activities are conducted in conjunction with the SELECT Initial and Randomization Visits to determine eligibility for PREADVISE. Participants who were randomized to SELECT prior to October 1, 2002 may be registered to PREADVISE: 1) at, or within 28 days following their first Six Month SELECT Visit, or 2) at, or within 28 days following their Annual SELECT Visit. These participants must meet the age requirement of 62 (60 if of African or Hispanic descent) at the time of registration to PREADVISE.

Prior to administration of any PREADVISE procedures, the potential participant will sign the PREADVISE informed consent. The participant will be asked to complete the Family History of Dementia (Form #310) and be evaluated for eligibility using the data on the Neurologic Medical History (Form #311). If the consented participant is potentially eligible he will then be given the Memory Impairment Screen (MIS). The MIS result must be greater than 4. Scores of 4 or lower on the MIS at the time of registration into PREADVISE will be exclusionary (possible prevalent case).

A modified Hachinski rating (risk of vascular dementia) will be completed by the PREADVISE Coordinating Center based on data from the Neurologic Medical History (Form #311) as well as additional information from physical exams, vital signs, other concurrent medications and laboratory data extracted from SELECT database.

7.3 Annual Visits

The annual visits for PREADVISE are concurrent with the SELECT Annual Visits and will include the administration of the MIS, and Neurological Medical Events (Form #313). In the event of a MIS score of 4 or less, an expanded mental status assessment with the CERAD tests (see Section 10.2) will be completed. If scores from the expanded evaluation are below cutoffs, a medical evaluation for dementia will be recommended to the participant and scheduled 4 to 6 weeks after the Annual Visit. Extension of this period may be granted, on a case-by-case basis, if discussed with and approved by the PREADVISE Investigators.

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7.4 Criteria for removal from protocol:

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

7.5 The participant will be followed as described in the main SELECT protocol (S0000).

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

Dose modifications will be performed as outlined in Section 8.0 of the main SELECT protocol (S0000).

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9.0 STUDY CALENDAR

Required Studies	Registration Visit*	Annual Visits
Memory Impairment Screen	X	X
Neurologic Medical History	X	
Family History of Dementia	X	
Neurologic Medical Events		X
Extended Mental Status (CERAD) †		If MIS < 4
Dementia Medical Evaluation †		If CERAD battery "failed"
Consensus Conference †		Following Medical Evaluation for Causes of Memory Impairment

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* The first PREADVICE visit will be in conjunction with the SELECT Initial and Randomization Visits, the first Six Month Visit, or first Annual Visit depending on when the participant is randomized to SELECT. See Section 5.1.

† See Section 10.0 for more information.

NOTE: All forms used in this study will be available via the SELECT Workbench. Forms completion and submission guidelines are found in Section 9 of the SELECT Study Manual.

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 The primary endpoint of this trial is the diagnosis of AD or other dementia at a moderate to severe level using National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association and Diagnostic and Statistical Manual-IV (DSM-IV) criteria by a consensus conference (see Appendix Section 19.1). Diagnosis will be obtained using the three-stage process described below.

10.2 Alzheimer's Disease Diagnostic Process

Stage 1: Cognitive Screening Using the MIS: Because several thousand men will be annually screened for AD, the MIS is used as the first stage screen due to its brevity (5 minute) and reasonable sensitivity and specificity. (1) A cutoff point of 4 (on an 8-point scale) will be used to stratify participants at this stage. All enrolled participants scoring above 4 on an Annual Visit MIS screening will return the following year for another MIS screening examination. A score of 4 or lower on an Annual MIS screening will indicate a need for the participant to proceed to the second stage CERAD battery of tests. These tests are necessary to evaluate for potential memory problems that were suggested by a low score on the MIS (See "Stage 2: Cognitive Screening Using the CERAD Tests" below).

Stage 2: Cognitive Screening Using the CERAD Tests: The second stage will consist of an expanded mental status examination using the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) battery of mental status tests (45 minutes). This battery includes:

- Mini Mental State Examination (MMSE),
- Short Blessed Test,
- 15-item Boston Naming Test,
- Word-list learning task,
- Verbal recognition task,
- Verbal fluency, and
- Constructional praxis tasks.

Each of these measures has been well standardized. Spanish/French versions are available and can be accessed from the SELECT workbench. (12, 24) The time required to complete this battery of tests is approximately 45 minutes and the site will be compensated for this time and for the submission of the forms to PREADVISE. Completed data forms from the CERAD evaluation will be faxed to the PREADVISE Coordinating Center where scoring of CERAD measures will be completed. A participant who scores 2 standard deviations below the normal mean on the MMSE or 2 standard deviations below the mean on at least one memory test and on one other test will meet the criteria for cognitive impairment or change in cognition and will proceed to Stage 3 (medical dementia evaluation and consensus conference) of the dementia screening process (see Medical Evaluation Section below). If a participant passes the CERAD screening, he will be reevaluated (starting with Stage 1: MIS) at the next annual SELECT visit.

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The CERAD tests are supplemented with the Geriatric Depression Scale to screen for depressive symptoms. (25) A score of 12 or higher on the GDS alone will result in a referral recommendation for an evaluation for depression.

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Because the CERAD battery of tests is for those participants who score 4 or lower on the MIS during an Annual Visit, these tests will not be needed until the first registered participants make their first annual return visit. The Study Site staff at the participating sites will be trained by PREADVISE staff to administer the CERAD tests through workshops during the semi-annual Southwest Oncology Group Meetings, beginning in October 2002. CERAD testing of the validation and normal aging subgroups will be done at SELECT sites that are associated with Alzheimer's Disease Centers (ADCs). Personnel at these ADCs are already familiar with administering these tests. The CERAD forms will then be forwarded to the PREADVISE Coordinating Center in Lexington, KY where they will be scored, and the scores interpreted by qualified PREADVISE staff.

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If the CERAD battery of tests indicate a memory problem, the SELECT and PREADVISE clinicians will encourage the participant to undergo a medical evaluation to rule out medical causes for his memory problems. If the site is near, or associated with, an ADC, we would suggest that the participant have the medical evaluation performed by the professionals at the ADC. For example, the ADC at the Sanders-Brown Center on Aging at the University of Kentucky will be available to perform dementia evaluations for sites located in Lexington, Louisville, and Ashland, KY; Cincinnati, OH; Johnson City and Nashville, TN; and Charleston, Clarksburg and Morgantown, WV. However, the participant is free to use his physician and facility of choice.

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PREADVISE receives no funding to provide medical services, so as with any medical needs, the participant will need to rely on Medicare or other insurance to cover the costs of medical tests and procedures associated with a medical or depression evaluation. Based on incident cases identified in the first 3 years of the study, we may apply for supplemental funding to assist uninsured persons with these evaluations. However, given that the majority of participants will be over the age of 65, Medicare coverage may apply to the majority of cases.

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If at any return visit the participant self-reports that he has been diagnosed with any form of dementia or that he is taking medications for the treatment of AD (donepezil, rivastigmine, galantamine), he will be administered the CERAD tests to verify the dementia diagnosis, or verify that he has memory problems. Medical records will be requested from the prescribing physician for consensus conference review by the PREADVISE clinicians. If the evaluation resulting in the prescription of AD medications is considered inconclusive or incomplete or he does poorly on the CERAD tests, he will be encouraged to undergo a medical evaluation to rule out metabolic causes for his memory problems.

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Stage 3: Medical Evaluation for AD: For participants who meet criteria for cognitive impairment or change in cognition at any assessment, a clinical evaluation will be completed following completion of the second PREADVISE consent form. This evaluation will incorporate a review of medical and family history, general neurological and physical examinations, brain imaging study (CT or MRI), and standard laboratory evaluation of blood (complete blood count, vitamin B12 and folate levels, thyroid function studies, rapid plasma regain, blood metabolic screen to include electrolytes, glucose, calcium, phosphorous, liver function studies, renal function studies, and total protein). This evaluation will be coordinated by PREADVISE Coordinating Center staff working with the participant's Study Site staff, private physician, or a dementia specialist (neurologist, geriatrician, neuropsychiatrist) at the SELECT Study Site. Data from this evaluation will be forwarded to the PREADVISE Coordinating Center for review. If AD or another dementia is diagnosed, the participant will be re-evaluated with the CERAD measures on an annual basis until the participant is no longer able to comply with the PREADVISE

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study procedures. These data will provide added clinical information of disease progression that will solidify the clinical dementia diagnosis. If dementia is not diagnosed, the participant will be followed with the proposed screening methods, starting with the MIS at the next SELECT Annual Visit.

10.3 Consensus Review for the Diagnosis of Dementia

Following the medical evaluation for dementia, a consensus group will review data at the University of Kentucky Alzheimer's Disease Research Center. This group is composed of three neurologists and two neuropsychologists with over 60 years of combined experience with clinical dementia assessment. The case will be presented to the group based on the evaluation that was completed by the local physician. These data will include the review of history, laboratory findings, physical and neurological examinations, MRI or CT scans, and mental status data. The DSM-IV criteria for diagnosis of dementia of the Alzheimer's type will be used. After the case has been reviewed, the group will generate a diagnostic summary. This summary will list the diagnosis(es), any need for additional data, and the degree of agreement between the clinicians. These data, in the form of a written summary, will be provided to the SELECT Study Site and the physician who completed the medical evaluation of the participant.

The diagnosis of other dementing disorders also will be determined in the Consensus Review Conference. For the diagnosis of dementia with Lewy bodies (DLB), the criteria of the Consortium on DLB International Workshop will be used. (9, 10) The key criteria include fluctuating cognitive decline, recurrent visual hallucinations and Parkinsonian features. Supportive features include repeated falls, syncopal episodes, neuroleptic sensitivity, and delusions. These criteria have been found to be valid in autopsied subjects. (10)

For the diagnosis of vascular dementia (VaD) the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* criteria will be used. (19) The essential components of the criteria are the presence of dementia, cerebrovascular disease clinically and by neuroimaging, and a causal link between the two. The clinical criteria for frontotemporal dementia that will be used are those described by Neary et al., although these criteria primarily consist of a list of clinical features and supportive investigations. (14) While they have not been well validated and do not establish diagnostic certainty, they are the best criteria available. The clinical criteria for progressive supranuclear palsy to be used are those described by NINDS-Society for Progressive Supranuclear Palsy International Workshop. (7) These criteria are relatively sensitive and accurate. The clinical criteria for primary progressive aphasia that will be used are those described by Mesulam and Weintraub. (11) Corticobasal degeneration (CBD) has proven to be a more difficult diagnosis and definitive consensus criteria have not been established. A study of the accuracy of the clinical diagnosis of CBD by neurologists revealed low sensitivity. (8) For this study, we will use an amalgam of the criteria described by Litvan, et al and the clinical findings from the largest clinical series. (8, 16) A number of other disorders causing dementia including prion disorders, post traumatic dementia, normal pressure hydrocephalus, Wernicke-Korsakoff syndrome, and metabolic disorders will be defined by the clinical manifestations, laboratory findings, and course of the disorder.

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10.4 Normal Screening Case Follow-up: Validation and Normal Aging Studies

The MIS is a relatively new screening tool. There is a need to more carefully determine the sensitivity and specificity of the MIS in a population-based sample. For this purpose, a validation group of 500 men who pass the MIS screening will be evaluated at a few SELECT sites affiliated with ADCs. This validation will occur in the first two years using the CERAD. This will allow us to compare their performance to those individuals who "failed" the MIS and CERAD tests for the determination of sensitivity and specificity of the screening approach. This is a one-time assessment.

Age is the greatest risk for AD. Certain mental functions have been reported in retrospective studies to predict a diagnosis of dementia. This trial therefore represents an excellent opportunity to evaluate age-associated changes in cognition. Therefore, 200 of the 500 men from the validation sample will be asked to complete the CERAD tests in each year of the project. These results will then be compared to those who receive the diagnosis of AD during the course of the project. In these 200 individuals, the mental status battery (CERAD) will be supplemented by these five other brief tests (20 minutes) that have been suggested as predictors of dementia:

Digit Symbol Substitution,
Trailmaking,
Controlled Oral Word Association (COWA-verbal fluency), and
Ruff 2&7 Test of Selective Attention
National Adult Reading Test (NART)

These tests will be administered and scored in the same manner as specified for CERAD (see above). These additional tests were selected on the basis that they provide an assessment of "usual" aging changes in cognition or processing speed. The Digit Symbol Substitution has also been reported to be a predictor of the evolution to dementia as well as overall memory performance. (3, 21) They also provide the most economical "paper and pencil" method for evaluating mental processing speed.

This evaluation of "usual" age-associated change, and the possible impact of APOE alleles and treatment on cognition, will involve those participants who were selected to complete the CERAD battery of tests after "passing" the initial MIS screening. Analyses will focus on the impact of the SELECT supplements on normal aging declines in these mental skills. These exploratory analyses will take place in Year 3 of the project, but data will continue to be collected through Year 5. If reliable changes, associations with cognition, or differences in change due to treatment arms emerge, we will apply for a supplement to this study to evaluate processing speed in more detail.

10.5 Secondary Endpoints

Diagnosis of other forms of dementia will be a consequence of the three stage screening process described above.

11.0 STATISTICAL CONSIDERATIONS

This trial will screen for AD among the subset of men aged 62 years or older (60 if of African descent or Hispanic) who are randomized to SELECT at participating Study Sites and who are cognitively intact at the time of randomization. It will then test the main hypothesis: use of both vitamin E and selenium will reduce the incidence of AD when compared to placebo (use of neither Study Supplement) among age cohorts for which the AD incidence curve is beginning to rise.

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We use a very conservative power calculation to show that a 40% reduction in the relative risk for AD is detectable with 80% power in this trial.

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This detectable difference is estimated using the following assumptions explained in more detail below. Adjustments for participant drop-outs, drop-in, adherence rates, mortality and loss to follow-up have been made and are the same as those for SELECT. AD incidence rates for men are interpolated from midpoint to midpoint of five-year age groups (see Table 1) based on the expected distribution for the participants on study. Finally, a two-tailed test of significance at the 0.05 level is assumed. Under these assumptions the detectable relative risk is 0.60 for 80% power (0.55 for 90% power).

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Based on scientific evidence (see Section 2.0, Background) and the fact that the Study Supplements are being administered very early in the incidence curve for this disease, it is not unreasonable to assume that the combined drugs will reduce the relative risk for AD by 40% or higher. This is a conservative calculation of a detectable difference for the following reasons: a) it relies on a two-tail test of significance when the main intent of the trial is clearly one sided (reduce incidence), and b) it is based on reliable but very conservative incidence figures for the disease.

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Secondary Comparisons:

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It is of interest to test the significance of the main effect of vitamin E (both vitamin E arms versus both vitamin E placebo arms) or the main effect of Se (both Se arms versus both Se placebo arms). Repeating the calculations above with double the sample size for testing a main effect, the proposed trial has 80% power to detect a relative risk of 0.69. The combination of vitamin E and Se has not been used together in trials of significant size populations. In addition, data are needed on the effects of low doses of vitamin E and Se over long periods (7 - 12 years) in relation to the potential of preventing Alzheimer's Disease.

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Number of Participants:

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The number of men available for testing this contrast was estimated using the randomization data from SELECT as of February 14, 2002. At that time 8,035 men were randomized to SELECT. The race and age-eligible distribution (60 for men of Hispanic or African descent, 62 for other races) is presented in the table below. Using a weighted averaged based on the race and age distribution, and a total accrual to SELECT of 32,400, it is estimated that approximately 17,600 men will be race/age eligible for PREADVISE.

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	Total (%)	Total (%) greater than age-cutoff
African American or Hispanic	1018 (12.7%)	439 (43.1%)
Other	7017 (87.3%)	3904 (55.6%)
Total	8035	4343

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If we assume that 40% of the potentially eligible do not participate in PREADVISE either because it is not implemented at a Study Site or because of individual participant refusals, there will be approximately 10,560 men enrolled in PREADVISE.

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AD Incidence Rate:

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The incidence rates used in the power calculations are based on data for men only and are taken from the publication by Rocca, et al. (17) These rates are listed in Table 3. Notice that these rates are comparable to the rates for both sexes combined available from a large number of incidence studies, provided the diagnosis of the disease is at a moderate or more severe level. (4, 6, 7, 18) These rates are conservative since they are derived from data on white men only, while a significant portion of the men recruited to the SELECT trial are expected to be of African descent or Hispanic who may have higher incidence rates. The incidence rates for older age cohorts are also needed because the surviving men will enter these age cohorts as the study progresses.

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Table 1: AD incidence in men per 1,000 person-years in Rochester MN: 1980-84 (18)

Age (years)	60 - 64	65 - 69	70 - 74	75 - 79	80 - 84	85 - 89	90 - 94
Men only	0.67	1.99	2.99	9.04	18.15	28.32	37.74

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Adherence Rate:

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Hazard depends on adherence, a time dependent covariate. It is quantified by the medication rate defined as the percent of full active drug taken by men in a specified arm. Power calculations assume that adherence rates for men on active drug declines from 100% at randomization to 51% at the end of twelve years. Estimates are based on prior experience in the PCPT trial with extrapolations from Year 4 of that trial to Year 12.

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Drop-in Rate:

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The drop in rate for placebo subjects to active medication is assumed to be 10% over the 12 years of study.

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Death and Loss to Follow-up:

Adjustments for mortality were obtained by using the Life Tables for Males in the United States. (13, see Table 2) The lost to follow-up rate is estimated to be 0.5% per year.

Table 2. Death Rate

Age	Caucasian	African Descent
60 - 61	0.012911	0.024429
61 - 62	0.014204	0.026635
62 - 63	0.015647	0.028529
63 - 64	0.017239	0.029814
64 - 65	0.018936	0.030629
65 - 66	0.020626	0.031094
66 - 67	0.022355	0.031759
67 - 68	0.024301	0.033184
68 - 69	0.026587	0.035871
69 - 70	0.029200	0.039779
70 - 71	0.032004	0.044606
71 - 72	0.034886	0.049628
72 - 73	0.037923	0.054390
73 - 74	0.041102	0.058025
74 - 75	0.044451	0.060562
75 - 76	0.047963	0.062781
76 - 77	0.051740	0.065477
77 - 78	0.056006	0.068659
78 - 79	0.061034	0.072931
79 - 80	0.066987	0.078545
80 - 81	0.074080	0.085445
81 - 82	0.082164	0.093270
82 - 83	0.090939	0.101910
83 - 84	0.099928	0.110349
84 - 85	0.109194	0.118075
85 - 86	0.119253	0.125451
86 - 87	0.129730	0.133095
87 - 88	0.141001	0.141104
88 - 89	0.153228	0.149498
89 - 90	0.166466	0.158249

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Data Analysis Plan:

All data analyses will be the same as those conducted in the SELECT protocol. Five interim analyses are planned, occurring 5, 7, 9, 10, and 11 years after the first participant is registered. Additional reports on the incident Alzheimer's disease cases without reference to treatment arm will be made in Years 3 and 4 (also for competing renewal of the grant) to the SELECT DSMC and the External Advisory Committee of PREADVISE (comprised of four experts in AD epidemiology). This committee will meet annually with PREADVISE investigators to review study progress.

The five interim analyses will test the main contrast of interest (a relative risk of 0.6) at the .0005 level using an extension of the log rank test that allows for testing a relative risk not equal to one. Since SELECT has its own Data and Safety Monitoring Committee it is possible that one of the arms could be closed by this time for reasons not connected to this study.

The final analysis will be completed within six months of the end of the trial. At this point, 294 - 329 AD incident cases will have been accrued depending on the magnitude of the reduction in incidence due to both vitamin E and Se. The log rank test will be used for each comparison of interest: main contrast of interest (compare the vitamin E plus Se arm with the double placebo arm) as well as the secondary contrasts (main effects of vitamin E and Se). Any other endpoints or contrasts of interest will be conducted at a 0.01 level of significance. The latter includes all forms of dementia, and overall mortality. Covariates such as APOE status and comorbid conditions will be included in the analysis to adjust for potential imbalances among the four arms. In addition, since a subsample of men passing the initial screen will also take the second stage screen, it will be possible to determine the robustness of the results using analyses suitable for longitudinal dementia studies with two-phase sampling designs. These analyses include an inverse probability weighting analysis, a full maximum likelihood analysis, and a mean score imputation analysis. (2) A recent selection model procedure of Gao, et al., will be also used to estimate the effect of non-ignorable missing data (due to deaths) on the estimation of incidence of AD and the comparison of the treatments. (5)

12.0 DISCIPLINE REVIEW

Discipline review criteria are included in Section 12.0 of the main SELECT protocol (**S0000**).

13.0 REGISTRATION GUIDELINES

Registration 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

Special instructions are included in Section 15.0 of the main SELECT protocol (**S0000**).

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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 Subjects (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 Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each investigational drug supplied for a study, drug disposition (drug receipt, dispensing, transfer or return) shall be maintained on the NCI Investigational Drug Accountability Record. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record; the ID # and initials of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned to the NCI or transferred to another NCI-approved protocol. These Drug Accountability Records must be readily available for inspection and are open to FDA or NCI inspection at any time.

Adverse Experiences

Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines in the main SELECT protocol (**S0000**). On Phase II and III studies, all deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by telephoning the Statistical Center.

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

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

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.

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18.1 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 Initial Model Informed Consent document for PREADVISE and a Secondary Consent Form – Medical Evaluation for Possible Memory Problems are enclosed and must be reviewed and approved by the institutional IRB before placing a participant on study.

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For IRB use only, not to be included in participant information.

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

Readability Statistics: Flesch Reading Ease 60.2 (targeted above 55)
 Flesch-Kincaid Grade Level 8.7 (targeted below 8.5)

S0000A, "Prevention of Alzheimer's Disease With Vitamin E and Selenium Trial (PREADVISE)," Initial Consent Form

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 a research study about how useful vitamin E and selenium might be for preventing memory changes with age (including Alzheimer's disease and other diseases that can affect the brain). You are being asked to take part in this research study because you are taking part in SELECT. SELECT is a study that looks at the use of vitamin E and selenium for preventing prostate cancer. African American and Hispanic men who are age 60 or older may take part. Men of other ethnic groups aged 62 or older may take part. The reason for this age difference is that Alzheimer's disease appears at younger ages in certain ethnic groups.

You should not take part in this study if any of the following apply:

1. You have been told you have an illness such as Parkinson's disease, Huntington's disease, Alzheimer's disease, any kind of dementia, brain tumor, seizures, stroke, multiple sclerosis;
2. You have been told you have a serious medical illness (such as cancer, liver, lung, blood, gallbladder or kidney disease);
3. You have been told you have a mental illness such as depression, anxiety, history of schizophrenia, alcohol or substance dependency; or
4. You take certain drugs that can affect memory and thinking.

The SELECT doctors or staff will review your medical history and drugs with you to verify that you have no condition(s) that would exclude you from this study.

WHY IS THIS STUDY BEING DONE?

The purpose of SELECT, in which you are taking part, is to see if there is a difference in finding prostate cancer between a group of healthy men who received selenium alone, vitamin E alone, selenium and vitamin E and placebo.

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Alzheimer’s disease (AD) is the most common adult onset memory disease. It affects over 4 million people in the United States. Scientists think that around 14 million people will have AD by the year 2050 unless a way to prevent it is found. Studies show that the chances of getting AD increase strongly after the age of 65. At present, no effective therapies are available for AD.

Studies show that increased oxidative stress (from excess free radicals) may damage brain cells and is linked with AD. Many studies show increased oxidation of brain lipids (fats), proteins, carbohydrates (sugars) and DNA in AD. Although the causes of AD are not known, it is believed that oxidative stress is part of what damages brain cells in AD and probably other brain diseases. For example, one study of vitamin E in 341 patients with AD showed mild slowing of the progression of this disease. Animal and tissue culture studies of vitamin E and selenium show that they can protect brain cells from damage.

This research is being done to see how safe and effective vitamin E and selenium may be in preventing AD and other brain illnesses. These illnesses are more common in people over the age of 60 to 65.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Participating in this study is your choice. About 10,000 men will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Each visit for PREADVISE will involve a short 5- minute exam of your memory, and questions about your medical history. If you agree to be in this study, your memory will be checked once each year. The 5-minute memory check will involve learning and remembering a short list of words. If the memory check suggests that you have memory changes, you will be asked to take a longer memory and thinking test. This may take an extra 45 to 60 minutes. It will involve a longer word list for you to learn and remember, naming pictures and drawing shapes. You will be asked to answer questions to check your language, word use and other skills as well as your mood.

If this second exam also suggests memory changes, you will be asked to see your family doctor, or a doctor identified by the SELECT or PREADVISE doctors, to complete a medical exam to find the possible causes of this memory change. This medical exam will be coordinated with you by the SELECT and PREADVISE staff. After the medical exam, one of the PREADVISE doctors will call you.

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They will talk with you and with a person who knows your day-to-day activities. If the second exam or doctor visit does not suggest memory and thinking changes, your memory will continue to be screened using the 5-minute check at the next yearly study visit.

If you are asked to complete a medical exam for memory changes, you will be given another consent form at that time. This will allow the results of the medical exam to be sent to the PREADVISE doctors for their review to help with diagnosis.

To check on the accuracy of the screening memory test, a smaller group of men (about 500) will be asked to complete the 45-minute exam, even though the memory screening did not suggest memory changes. This request will be determined by chance (such as a coin flip). If you agree, you will then be asked to continue to take both the screening and 45-minute memory and thinking tests each year. The results of these memory checks will not affect your participation in SELECT.

WHAT ELSE MIGHT YOU BE ASKED TO DO?

You may also be asked to be part of a group of 200 of these 500 men who will be asked to volunteer to continue to take both the 5-minute memory screening and the longer set of memory and thinking tests each year, plus five additional brief tests. This may take an additional 45 to 60 minutes during each Annual Visit. It involves a longer word list for you to learn and remember, naming pictures, drawing shapes, and questions to check your language, vocabulary, awareness skills, and mood. This request will be determined by chance (such as a coin flip). The results of these memory checks will not affect your participation in SELECT.

The results of the memory checks will not be given to you. If you do have a medical workup for memory changes, this information will be given to your doctor after your medical workup is completed.

At the start of the SELECT study you may have allowed a blood sample to be collected for future testing. The confidentiality and risk information related to this activity have been explained in the main SELECT consent form. This blood sample was stored by SELECT. For the PREADVISE study, part of this sample may be tested for a genetic risk factor associated with Alzheimer's disease, called Apolipoprotein E (ApoE). The results of this test will be used for research purposes only and you will not be told the results of this test. The ApoE information will be used to compare changes over time that might be associated with ApoE status. Even if you did not give a blood sample or did not consent to storage and testing of your blood sample, you may still participate in PREADVISE.

1110

1111 **HOW LONG WILL I BE IN THE STUDY?**

1112 The research exams will be done at the clinic where you are taking part in SELECT.
1113 There will be one study visit for each year that you are in SELECT (7 to 12 visits).
1114 These PREADVISE visits will take place during SELECT visits.
1115

1116 **WHAT ARE THE RISKS OF THE STUDY?**

1117 **Memory and thinking tests present practically no risk. The potential risks**
1118 **are small. You may have tiredness or fatigue from the testing. If you have**
1119 **any discomfort, you are free to stop at any time.**

1120
1121 **If you develop problems with memory and thinking during this study, you**
1122 **can choose medical testing and treatment through your family doctor, a**
1123 **specialist of your choice, or a specialist identified by the SELECT and**
1124 **PREADVISE doctors. The finding of any problems in memory and thinking**
1125 **will be made by the PREADVISE doctors' review of your study**
1126 **and medical records. If they think that there has been a change based on the**
1127 **memory and thinking tests used in this study, they and the SELECT**
1128 **doctors will tell you about your options for a medical workup. This may**
1129 **result in feelings of stress and anxiety about your health until the medical**
1130 **checkup is completed.**

1131
1132 **For more information about risks and side effects, ask the researcher or**
1133 **contact _____.**

1134
1135

1136 **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

1137 **There is no guarantee that you will get any personal benefit from taking**
1138 **part in this study. However, it may be possible that the early detection of**
1139 **memory changes can lead to early diagnosis and treatment. You may also**
1140 **decrease your risk of getting AD, if the supplements are effective and you**
1141 **are taking them as part of SELECT. The findings of this study may also**
1142 **help in our understanding of Alzheimer's disease and may help other**
1143 **people with this disease in the future.**

1144
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1146 **WHAT OTHER OPTIONS ARE THERE?**

1147 **If you choose not to take part in PREADVISE, but remain in SELECT, you**
1148 **have these other options:**

1149
1150 **Some vitamin companies are selling other nutrients as supplements for**
1151 **memory. You may buy these supplements at your own expense without**
1152 **being in PREADVISE. However, the supplements must not contain vitamin**
1153 **E or selenium if you are in SELECT.**

1154
1155 **You can also have memory checkups by your family doctor. All of the**
1156 **checkups on this study may be available at this center or at other locations.**
1157 **Please talk to your regular doctor about these and other options.**

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1159

1160 WHAT ABOUT CONFIDENTIALITY?

1161 Efforts will be made to keep your personal information confidential. We cannot
1162 guarantee absolute confidentiality. Your personal information may be disclosed if
1163 required by law.

1164
1165 Organizations that may inspect and/or copy your research records for quality
1166 assurance and data analysis include groups such as: the National Cancer Institute,
1167 the Sanders-Brown Center on Aging at the University of Kentucky, the Food and
1168 Drug Administration, the National Institute on Aging; the makers of vitamin E,
1169 selenium and placebo pills for the study, and the Southwest Oncology Group.

1170
1171 If we publish the information we learn from this study in a medical journal, you will
1172 not be identified by name or in any other way.

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1174

1175 WHAT ARE THE COSTS?

1176 Taking part in this study may lead to added costs to you or your insurance. Added
1177 costs may be due to finding AD or other diseases that cause memory loss at your
1178 examination. For example, your doctor may suggest a medical workup if you have
1179 an abnormal memory exam. These costs are discussed further below. Please ask
1180 your nurse or doctor about any expected added costs.

1181
1182 In the case of injury or illness resulting from this study, emergency medical
1183 treatment is available but will be provided at the usual charge. No funds/funds have
1184 been set aside to compensate you in the event of injury. (*local institutions must*
1185 *choose the option that best fits the hospital's situation*)

1186
1187 You or your insurance company will be charged for continuing medical care and/or
1188 hospitalization.

1189

1190 You will receive no payment for taking part in this study.

1191

1192 **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

1193 Taking part in this study is voluntary. You may choose not to take part or may leave
1194 the study at any time. You may decline or stop taking part in PREADVISE without
1195 any effect on your participation in SELECT. Leaving the study will not result in any
1196 penalty or loss of benefits to which you are entitled. You can stop participating at
1197 any time. However, if you decide to stop participating in the study, we encourage
1198 you to talk to the researcher and your regular doctor first.

1199

1200 A Data Safety and Monitoring Board, an independent group of experts, will be
1201 reviewing the data from this research throughout the study. We will tell you about
1202 important new information from this or other studies that may affect your health,
1203 welfare, or willingness to stay in this study.

1204

1205

1206 **WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

1207 The persons in charge of this study are Drs. William Markesbery, Frederick
1208 Schmitt and Richard Kryscio of the Sanders-Brown Center on Aging at the
1209 University of Kentucky.

1210

1211 For questions about the study or a research-related injury, contact the researcher _
1212 NAME(S) at TELEPHONE NUMBER .

1213

1214 For questions about your rights as a research participant, contact the NAME OF CENTER
1215 Institutional Review Board (which is a group of people who review the research to
1216 protect your rights) at TELEPHONE NUMBER . [And, if available, list participant
1217 representative (or other individual who is not on the research team or IRB).]

1218

1219

1220 **WHERE CAN I GET MORE INFORMATION?**

1221 *[To IRB/Investigators: Attach information materials and checklist of attachments.*
1222 *Signature page should be at the end of package. You may also wish to include the*
1223 *following informational resources]*

1224

1225 PREADVISE: www.mc.uky.edu/preadvise

1226

1227 The Alzheimer's Association U.S.: www.alz.org

1228

The Alzheimer's Association Canada: www.alzheimer.ca

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You may call the NCI's Cancer Information Service at
1230 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

1231
1232 Visit the NCI's Web sites...
1233 cancerTrials: comprehensive clinical trials information <http://cancertrials.nci.nih.gov>.
1234
1235 CancerNet™: accurate cancer information including PDQ
1236 <http://cancernet.nci.nih.gov>.
1237
1238 You will get a copy of this form. You may also request a copy of the protocol (full
1239 study plan).
1240
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1244

1242 **SIGNATURE**

1243

1246 You are deciding whether or not to take part in this study. If you sign, it means that
1247 you have decided to volunteer to take part in this study, and that you have read and
1248 understood all the information on this form.
1249 **My consent to participate in SELECT has been provided in a separate**
1250 **document.**

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1254 Participant _____ Date _____

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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 53.9 (targeted above 55)
 Flesch-Kincaid Grade Level 9.5 (targeted below 8.5)

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S0000A, "Prevention of Alzheimer's Disease With Vitamin E and Selenium Trial (PREADVISE)," Secondary Consent Form – Medical Evaluation for Possible Memory Problems

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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.

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You are being asked to take part in this research study because you are taking part in PREADVISE. PREADVISE is a study that looks at the use of vitamin E and selenium for preventing Alzheimer's disease and other memory diseases.

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WHY IS THIS STUDY BEING DONE?

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As part of PREADVISE, you have been having regular memory checkups. At this time, these memory checkups suggest that you may be having memory changes. Therefore, you are being asked to have a medical workup. Your doctor or a specialist that you can choose with help from the SELECT and PREADVISE doctors can do this workup to see if the memory change suggested by the checkup is related to a medical condition. The results of this testing will be used for medical diagnosis as well as for the PREADVISE research project.

1289

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

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1291
1292

Participating in this study is your choice. If you volunteer to take part in this study, we think you will be one of about 300 to 500 men who may need this testing during their participation in PREADVISE.

1293

1294 **WHAT IS INVOLVED IN THE STUDY?**

1295 The medical evaluation for possible causes of memory problems will take place in
1296 your doctor's office. This will take about an hour of your time. Your doctor also
1297 will order a brain scan (computerized tomography (CT) or magnetic resonance
1298 imaging (MRI)) that may take up to 30 minutes. The total amount of time you will
1299 be asked to spend for this medical workup is about one to two hours.

1300
1301 This medical examination will involve a review by your doctor of your medical
1302 history, medicines, a physical and neurological exam, and blood and urine tests. If
1303 you agree to this part of the study, your medical test results will also be sent to the
1304 PREADVISE doctors for their review of possible causes of memory change.

1305
1306 If the information from this medical examination or doctor visit does not suggest a
1307 medical cause for memory changes, your memory will continue to be screened using
1308 the 5-minute check at the next yearly SELECT study visit. If a diagnosis of a
1309 dementia results from this medical examination, you will be asked to continue to
1310 take both the screening and 45-minute memory and thinking tests each year that you
1311 stay in PREADVISE and SELECT.

1312

1313 **WHAT ARE THE RISKS OF THE STUDY?**

1314 Medical evaluations for possible causes of memory changes present practically no
1315 risk. The potential risks or discomforts are small. You may experience tiredness or
1316 fatigue from the evaluation. A Magnetic Resonance Imaging (MRI scan) may cause
1317 possible anxiety due to the loud banging made by the machine and the confined
1318 space of the testing area. People with pacemakers, aneurysm clips, artificial heart
1319 valves, ear implants, or metal/foreign objects in their eyes are not permitted to
1320 undergo an MRI, but may have a Computed Tomography (CT scan). A CT scan
1321 involves exposure to a small amount of radiation. The amount of exposure is less
1322 than 1,000 millirems. (An individual living in a city receives about 100 millirems per
1323 year). Risks associated with the drawing of blood include soreness, bruising,
1324 infection, bleeding, pain, and lightheadedness or fainting. In total, less than three
1325 tablespoons of blood will be taken, and your body will quickly make up for this loss.
1326 There is also a risk that the medical exams will not be able to find a cause for your
1327 memory and thinking changes. However, if the cause is Alzheimer's Disease,
1328 medical diagnosis is correct 95 out of 100 times (95%) with this type of exam.

1329

1330 For more information about risks and side effects, ask the researcher or contact
1331 _____.

1332

1333 **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

1334 There is no guarantee that you will get any personal benefit from participating in this
1335 part in this study. However, it may be possible that the early diagnosis of medical
1336 conditions that cause memory change can lead to effective early treatment for your
1337 condition.

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1340 **WHAT OTHER OPTIONS ARE THERE?**

1341 **If you choose not to take part in PREADVISE, but remain in SELECT, you**
1342 **have these other options:**

1343

1344 **You may choose not to have memory checkups at all. You can have memory**
1345 **checkups by your family doctor. All of the checkups on this study may be**
1346 **available at this center or at other locations. Please talk to your regular**
1347 **doctor about these and other options.**

1348

1349

1350 **WHAT ABOUT CONFIDENTIALITY?**

1351 Efforts will be made to keep your personal information confidential. We cannot
1352 guarantee absolute confidentiality. Only your doctor and the PREADVISE and
1353 SELECT doctors will see the results of your medical examination. Your personal
1354 information may be disclosed if required by law.

1355

1356 Organizations that may inspect and/or copy your research records for quality
1357 assurance and data analysis include groups such as: the National Cancer Institute,
1358 the Sanders-Brown Center on Aging at the University of Kentucky, the Food and
1359 Drug Administration, the National Institute on Aging; the makers of vitamin E,
1360 selenium and placebo pills for the study and the Southwest Oncology Group.

1361

1362 If we publish the information we learn from this study in a medical journal, you will
1363 not be identified by name or in any other way.

1364

1365

1366 **WHAT ARE THE COSTS?**

1367 Taking part in the medical examination for causes of memory change will lead to
1368 added costs to you or your insurance. Added costs may result from blood studies,
1369 urine studies, brain scans, and doctor examinations needed to determine a cause for
1370 your memory loss. For example, your doctor may suggest other medical tests if
1371 you have an abnormal blood test. Please ask your nurse or doctor about any
1372 expected added costs.

1373

1374 In the case of injury or illness resulting from this study, emergency medical treatment is
1375 available but will be provided at the usual charge. No funds/funds have been set aside to
1376 compensate you in the event of injury. (*local institutions must choose the option that*
1377 *best fits the hospital's situation*)

1378
1379 You or your insurance company will be charged for continuing medical care and/or
1380 hospitalization.

1381
1382 You will receive no payment for taking part in this study.

1383

1384 WHAT ARE MY RIGHTS AS A PARTICIPANT?

1385 Taking part in this study is voluntary. You may choose not to take part or may leave the
1386 study at any time. Leaving the study will not result in any penalty or loss of benefits to
1387 which you are entitled. You can stop participating at any time. However, if you decide to
1388 stop participating in the study, we encourage you to talk to the researcher and your
1389 regular doctor first.

1390
1391 A Data Safety and Monitoring Board, an independent group of experts, will be
1392 reviewing the data from this research throughout the study. We will tell you about
1393 important new information from this or other studies that may affect your health,
1394 welfare, or willingness to stay in this study.

1395

1396 WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

1397 The persons in charge of this study are Drs. William Markesbery, Frederick Schmitt
1398 and Richard Kryscio of the Sanders-Brown Center on Aging at the University of
1399 Kentucky.

1400
1401 For questions about the study or a research-related injury, contact the researcher _
1402 NAME(S) at TELEPHONENUMBER.

1403

1404 For questions about your rights as a research participant, contact the NAME OF CENTER
1405 Institutional Review Board (which is a group of people who review the research to
1406 protect your rights) at TELEPHONENUMBER. [*And, if available, list patient representative*
1407 *(or other individual who is not on the research team or IRB).*]

1408

1409 WHERE CAN I GET MORE INFORMATION?

1410 [*To IRB/Investigators: Attach information materials and checklist of attachments.*
1411 *Signature page should be at the end of package. You may also wish to include the*
1412 *following informational resources]*

1413

1414 PREADVISE: www.mc.uky.edu/preadvise

1415

1416 The Alzheimer's Association U.S.: www.alz.org

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The Alzheimer's Association Canada: www.alzheimer.ca

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).

1436 SIGNATURE
1437

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1439

1440 You are deciding whether or not to take part in this study. If you sign, it means that
1441 you have decided to volunteer to take part in this study, and that you have read and
1442 understood all the information on this form.
1443 **My consent to participate in SELECT and PREADVISE has been provided**
1444 **in a separate document.**

1445
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Signature of person agreeing to take part in the study

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1454

Printed name of person agreeing to take part in the study

1455

1456

1457

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1459

Name of person providing information to participant

1460

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Signature of Investigator

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19.0 **APPENDIX**

19.1 DSM-IV Criteria for Dementia of the Alzheimer's Type

1478 19.1 DSM-IV Criteria for Dementia of the Alzheimer's Type

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A. The development of multiple cognitive deficits manifested by both:

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(1) memory impairment (impaired ability to learn new information or to recall previously learned information)

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(2) one (or more) of the following cognitive disturbances:

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(a) aphasia (language disturbance)

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(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

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(c) agnosia (failure to recognize or identify objects despite intact sensory function)

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(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

1494
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B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

1496
1497

C. The course is characterized by gradual onset and continuing cognitive decline.

1498
1499

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

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1501

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

1502
1503

(2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B₁₂ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)

1504
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(3) substance-induced conditions

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E. The deficits do not occur exclusively during the course of a delirium.

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F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

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