TITLE:
Study of Low Dose Whole Brain Irradiation in the Treatment of Alzheimer's Disease

NCT02359864

Protocol Approval date: 03/21/2022

Study Protocol with appendices and Statistical Analysis Plan

Title: **PHASE I FEASIBILITY STUDY OF LOW DOSE WHOLE BRAIN IRRADIATION IN THE TREATMENT OF ALZHEIMER'S DISEASE**

Version: **2.2**

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Schema

For Patients with Probable Alzheimer's Disease based on NINCDS-ADRDA Criteria and having MMSE scores of between 10 - 20	
Number of Patients	30
Randomization	N/A
Screening/Baseline Testing	The following tests/evaluation will be completed prior to initiation of treatment 1) MMSE 2) ADAS-Cog 3) History and Physical 4) Amyvid PET Scan 5) Toxicity Evaluation using CTC version 5.0/RTOG for following sites Skin, Eye, Ear and CNS 6) QOL-AD and QUALID assessment
Imaging Requirements	An Amyvid PET Scan will be required prior to treatment and at 4 months following completion of therapy. These scans will be read by the study designated board certified nuclear radiologist.
Treatment Procedure	Patients will receive whole brain irradiation using standard external beam techniques. The initial 15 patients will be treated at Dose Level 1 (5 x 200 cGy). If after the last patient in the first treatment group has been followed for 12 months and there have been no events that cause stoppage of the trial, the second group of patients will be enrolled at Dose Level 2 (10 x 200 cGy). All patients will receive 1 treatment per day on consecutive days excluding weekends
Trial Visits and Follow-Up	All patients will be followed as per Study calendar. Scheduled post treatment visits are at 6 weeks 3, 4, 6, and 12 months

Stopping Rules	This Study will be stopped for any of the following reasons 1) Any patient death attributed to treatment 2) Any patient who develops a Grade IV adverse event 3) More than 3 of 15 patients who develop a Grade 3 adverse event as per CTCAE v.5.0 in either group 4) 50% or more of patients in either group have no change or increase in amyloid based on Amyvid PET Scan 5) 5 patients that show greater than 4 point deterioration in MMSE in two consecutive cognition evaluations 6) 5 patients that show mean increases greater than 7 on ADAS-Cog scale.
Data Safety Monitoring Board (DSMB)	This trial will utilize a DSMB consisting of three physicians and one biostatistician who are not directly involved in the trial but who have expertise in radiation, Alzheimer's management, or both. They will meet monthly to review all new data that has been collected on any patient under treatment or in follow up and report quarterly to the IRB.
Treatment Groups	There will be two dose levels: 1) 5 x 200 cGy 2) 10 x 200 cGy
Trial Duration	12 month follow up following completion of therapy for each individual.

Abbreviations

AD	Alzheimer' Disease
Aβ	amyloid-beta
FDA	Food and Drug Administration
AβPP	amyloid-β precursor protein
BBB	blood–brain barrier
RT	radiation therapy
Gy	Gray
PCI	Prophylactic cranial irradiation
H&E	hematoxylin and eosin
BED	biological effective dose
SD	standard deviation
LET	linear energy transfer
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET	positron emission tomography
CTCAE v. 4.0	Common Toxicity Criteria for Adverse Events
RTOG/EORTC	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer
MMSE	Mini Mental State Examination
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
QOL-AD	Quality of Life- Alzheimer's Disease
QUALID	Quality of Life in Late Stage Dementia
SCLC	small cell lung cancer
IRB	Institutional Review Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder, Fourth edition
CBCT	cone beam computed tomography
HVL	half-value layer
DSMB	Data Safety Monitoring Board

1.0 Background and Rationale

1.1 Current and Future Incidence of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia among the elderly and affects over five million individuals in the United States [1]. Approximately 200,000 people younger than 65 years with AD comprise the younger onset AD population; 5 million are age 65 years or older. By mid-century, fueled in large part by the baby boom generation, the number of people living with AD in the United States is projected to grow by about 9 million [2]. In 2010, official death certificates recorded 83,494 deaths from AD, making AD the sixth leading cause of death in the United States and the fifth leading cause of death in Americans aged 65 years or older. Between 2000 and 2010, the proportion of deaths resulting from heart disease, stroke, and prostate cancer decreased 16%, 23%, and 8%, respectively, whereas the proportion resulting from AD increased 68%. The actual number of deaths to which AD contributes (or deaths ***with*** AD) is likely much larger than the number of deaths ***from*** AD recorded on death certificates. In 2014, an estimated 700,000 older Americans will die with AD, and many of them will die from complications caused by AD [2].

Data from the Framingham Study were used to estimate lifetime risks of AD and any dementia [3]. The study found that 65-year-old women without dementia had a 20% chance of developing dementia during the remainder of their lives compared with a 17% chance for men. For AD specifically, the estimated lifetime risk at the age of 65 years was nearly one in six (17.2%) for women compared with nearly 1 in 11 (9.1%) for men. There is a clear relationship between increasing age and AD. The number of Americans surviving into their 80s, 90s, and beyond is expected to grow dramatically because of advances in medicine and medical technology, as well as social and environmental conditions. By 2030, the segment of the US population aged 65 years and older is expected to grow dramatically, and the estimated 72 million older Americans will make up approximately 20% of the total population.

1.2 Pathophysiology of Alzheimer's Disease

The pathophysiology of AD develops over many years. The major pathological hallmarks are the accumulation of senile amyloid-beta (Aβ) plaques [4,5] and the development of insoluble neurofibrillary tangles of tau protein [6]. Aβ is produced by the proteolytic cleavage of Aβ precursor protein (AβPP) by β- and γ-secretases [7,8]. The abnormal processing and accumulation of Aβ initiates a cascade of events that culminates in neuronal damage and dementia [9-12]. In late-onset AD, the amount of Aβ that accumulates can be ~100–200-fold higher than normal [13]. The most recognized hypothesis [14] proposes that AD can be attributed to an imbalance between the production and clearance of Aβ, although Aβ clearing is not necessarily accompanied by cognitive improvement [15,16]. Aβ folding [17] and neuro-inflammation [18] may also be important in AD progression. The AD inflammatory response is associated with both neurodegeneration and neuronal survival with tissue repair [18-21].

1.3 Current Treatments for Alzheimer's Disease

The U.S. Food and Drug Administration (FDA) has approved five medications to treat the symptoms of Alzheimer's disease. donepezil, rivastigmine, galantamine, memantine and the combination of donepezil and memantine. The first three are acetylcholinesterase inhibitors that enhance the neurotransmission of acetylcholine in the brain, which is thought to be essential for cognition. There are many other strategies that have been studied for AD treatment including immunologic, nutraceutical, mitochondrial, phosphodiesterase, 5-HT6 receptor agonists and stem cell-based treatments [22]. The results from large-scale randomized clinical trials of pharmacological agents have been modest and it is clear that AD has multiple risk factors and is likely to have multiple pathogenic pathways. AD is not a one-gene, one-protein disease and should be attributed to a network of interactions between genes, proteins, organelles, cells, neurotransmitters, and the environment. Those disease-modifying agents currently being developed typically target one hypothesis and one protein. Thus, it is clear that a single drug for the successful treatment of AD is not yet available.

1.4 Background and Rationale for Radiation Treatment of AD

Eliminating amyloid-β has been advocated as a beneficial treatment strategy for AD patients, and anti-amyloid therapies remain a rational approach for preventing or delaying AD [23]. Amyloid-β is produced by the proteolytic cleavage of amyloid-β precursor protein (AβPP) by β- and γ-secretases and many novel pharmaceuticals are being developed to prevent the initial cleavage of AβPP [24,25]. The blood–brain barrier (BBB) has limited or thwarted the success of many of these agents either by preventing the drugs from initially crossing into the brain, or by ensuring the rapid removal of those drugs that can cross the BBB [26]. Delivery of an anti-amyloid therapy that is independent of the blood–brain barrier would be a promising new approach. One strategy not investigated previously for the treatment or elimination of amyloid-β plaques associated with AD is ionizing radiation therapy (RT). Radiation therapy has been shown previously to reduce amyloid-like deposits in extra-cranial disease sites [27-29].

Ionizing RT has not been considered previously for AD patients because of the potential to exacerbate cognitive impairment. The potential for side effects from brain RT are dependent on the total radiation dose given. Total doses of 30–60 Gy given in 2 Gy fractions can produce macroscopic tissue destruction [30] and impair cognition [31-35]. However, only minimal cognitive effects are produced (minor compared with the normal cognitive decline associated with AD) if the total dose remains low and critical brain structures are spared using image-guided RT. The severity of cognitive impairment depends upon the dose delivered to the medial temporal lobes, the site of the hippocampus [36]. Changes are evident using single doses of 5 Gy or higher [32-34], although 2 Gy produced no cognitive deficit [34]. Prophylactic cranial irradiation (PCI) [37], to a total dose of 12–20 Gy in 2 Gy fractions given daily, has become the standard-of-care for selected groups of adult patients with small cell lung cancer and in pediatric leukemia patients to decrease CNS relapse[38], with no [39,40], mild [41,42] or moderate [43] cognitive impairment. Moreover, whole brain RT can lead to the recruitment of protective glial cells that would be beneficial in an AD patient [33], and the use of recognized protectors or mitigators of RT damage would provide additional clinical safeguards [33,44-48]. Therefore, RT is a potential novel treatment option for AD that could be rapidly and

inexpensively implemented, especially when compared to the time needed and costs associated with developing new pharmaceuticals that are often only partially effective.

1.5 Preclinical Data Utilizing Radiation Treatment for Alzheimer's Disease

1.5.1 Effect of Radiation on Amyloid β Plaque Burden

The preclinical studies described in section 1.5.1 and 1.5.2 have been accepted for publication [49]. We used an established double transgenic model of AD namely, male B6.Cg-Tg (APPswe,PSEN1dE9)85Dbo/J mice. These mice express a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9), both directed to CNS neurons. Both mutations are associated with early-onset Alzheimer's disease. In initial proof-of-principle experiments, 30 6-month–old mice were randomized into groups (n=3-6 per group) and the right half of the brain X-irradiated at room temperature with either a single dose of 5Gy, 10Gy or 15Gy and sacrificed either 2, 4 and 8 weeks later. In subsequent studies, animals were treated with three different low-dose schedules 1Gyx10, 2Gyx5 or 2Gyx10. To assess the effects of treatments, coronal tissue sections (5μm) were cut from the harvested, formalin-fixed brains and mounted for antibody-specific immunohistochemistry of amyloid-β (Aβ), standard hematoxylin and eosin (H&E) for morphology and Nissl staining to assess neuronal cell density. Three stained coronal slices per mouse were analyzed to compare the number and size of beta-amyloid plaques in the irradiated versus untreated sides of the brain. Aβ plaques were counted and analyzed using an image analysis approach. By using a hemi-brain irradiation approach, we were able to overcome the inherent variability in Aβ plaques between animals as each animal served as its own control by comparing the irradiated side of the brain to the unirradiated side of the same brain (Figure 1). The percent change in plaque number between the irradiated and unirradiated side of the brain after Hemi-Brain Radiotherapy (HBRT) therefore indicated the true effect of the radiation treatment irrespective of the initial number of plaques that were present. The largest percent decrease in Aβ plaques was seen with the 5x2 Gy dose regimen (Table 1). Moreover, the size of the remaining Aβ plaques was smaller in the irradiated sides of the brain. At 4 weeks, the average decrease in Aβ plaque size was 13.8% (p=0.045), 17.2% (p= 0.021), 27.6% (p=0.011), 29.3% (p=0.005) and 28.7% (p=0.049) for animals given 5 Gy, 10 Gy and 15 Gy, 10x1 Gy and 5x2 Gy hemi-brain irradiation respectively. Single dose treatments and fractionated treatments can be mathematically

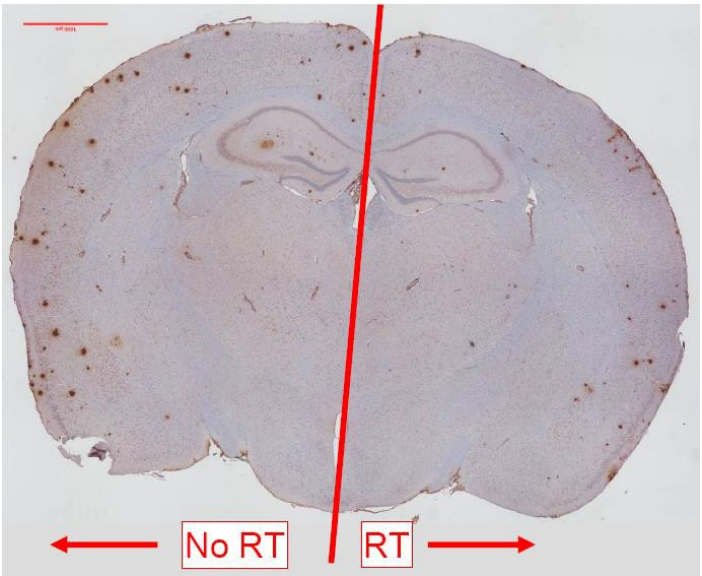

Figure 1: The right side in this coronal image was irradiated [RT]. The left side was not exposed [no-RT]. Fewer plaques are present on the RT side of the brain. 5x2 Gy was given and assessed at 4 weeks post RT.

	5Gy		10Gy		15Gy		1Gyx10		2Gyx5		2Gyx10	
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2 weeks	26.2	23.9	32.8	12.5	41.2	17.6						
4 weeks	29.3	13.1	45.7	33.6	56.9	33.2	50.6	3.2	71.8	23.4	78.5	14.5
8 weeks	21.5	14.2	54.2	19.3	68.2	14.3						

Table 1: Mean percent decrease in the number of Aβ plaques in the whole brain (cortex and hippocampus regions combined) for each **hemi-brain** RT regimen and assessment time. The size of the reduction in Aβ is dependent on the RT dose and assessment time. The percent decrease was calculated for each animal individually by comparing the plaque count between the irradiated and unirradiated sides of the brain, and then the mean and standard deviation (SD) percent reductions were calculated for each treatment group consisting of 3 animals. This analysis method is independent of the initial number of Aβ plaques present.

compared using the biological effective dose (BED) [50]. A larger percentage reduction is evident after the low-dose fractionated regimes compared with the single dose treatments. For example, a 29.3% (SD±13.1) reduction in Aβ plaques was seen after a 5Gy single dose (BED=17.5Gy) compared with 50.6% (SD±3.2) and 70% (SD±23.4) reductions after the 1Gyx10 (BED=15Gy) and 2Gyx5 (BED=20Gy) respectively. The most effective schedule was 2Gy x 10 (BED=30Gy) where the plaque reduction was 78.5%. This BED comparison clearly demonstrates a more pronounced reduction in Aβ plaque number with fractionation compared with larger single dose treatments.

All radiation treatments were well-tolerated and no post-radiation behavioral changes were observed, suggesting negligible or limited radiation-induced effects on normal brain tissues over the time course of the experiment. In addition, histological examination of the H&E stained tissue sections indicated no evidence of a significant decrease in cell density and no compelling evidence of significant cellular necrosis. No signs of devitalization, malacia or spongiosus or classic acute or chronic inflammatory features were seen in the tissue sections, confirming that the radiation doses were insufficient to produce notable cellular effects on normal tissues. A comparison of neuronal cell density from Nissl stained brain tissue sections indicated little difference in number of neuronal cells between the irradiated right-side and unirradiated left side of the brain, irrespective of dose or time post-treatment.

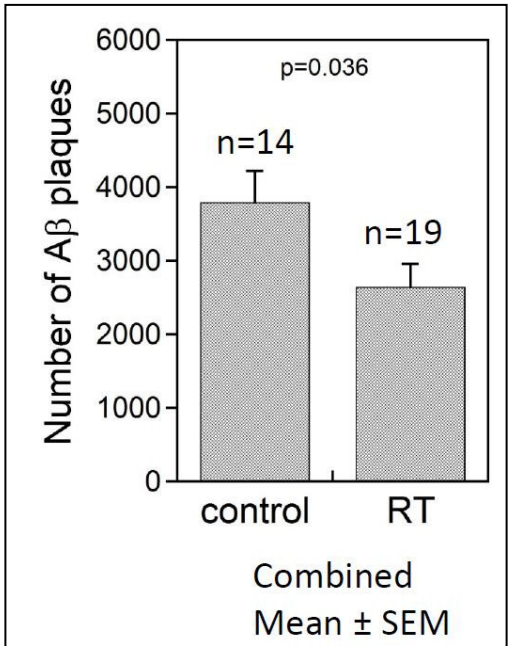

Figure 2: 64-week-old whole-brain irradiated animals had significantly lower numbers of Aβ plaques at 8-9 weeks after irradiation with 5 x 2 Gy than sham-treated animals.

1.5.2 Effect of Radiation on Cognitive Performance

The histology data suggested that there were no microscopic effects of low dose radiation on the brain; this was taken further in the next phase of the research by studying cognitive function after low dose radiation treatment. These experiments were

performed in collaboration with an independent group of Psychology scientists in a strict blinded-fashion and treatment groups were unknown to the individuals conducting the cognitive testing. 64-week old male mice were given **whole-brain** irradiation (n=19) or sham-treated exposures (n=14) and evaluated 8 weeks later. Figure 2 shows the plaque burden of these animals. The average number of plaques in the unirradiated cortex of the brain at 73 weeks was 3787 (SD ±1552; n=14), with a numerical range of 1777-6554 and median of 3560. The average number of plaques in the cortex of an irradiated brain was 2642 (SD ±1379; n=19), with a numerical range of 512-4695 and median of 2677. Daily irradiated with 2 Gy for five consecutive days with reduced the mean number of plaques (p=0.036). Average plaque size also decreased following irradiation from 42.95μM (SD ±12.8) to 14.52 μM (SD ±11.6). Spatial learning and memory were assessed in a Morris maze protocol over two 5-day periods, once before treatment (5 days prior to RT) and once after treatment (8 weeks after RT). The mice were trained to locate a platform submerged in a pool of opaque water (22°C±1°C) in 3 trials/day with a 30-min inter-trial interval over 5 consecutive days. Latency to find the platform was measured. Eight weeks following RT mice were retested. Prior to whole-brain irradiation, the group of animals to be treated with 2Gyx5 (*Mean (M)* = 48.67 secs, *SD* = 15.63 secs) and the untreated group (*M* = 58.07, *SD* = 23.34) did not differ significantly in latency to find the platform across trials on the final testing day (day 5), p =0.399. Following irradiation, the treated mice showed no deficits in spatial learning and memory relative to the control group prior to treatment, again suggesting negligible or limited radiation-induced effects on normal brain functioning. Conversely, the treated group displayed significantly reduced latencies (*M* = 30.96, *SD* = 17.64) compared to the untreated group (*M* = 53.93, *SD* = 14.92) across trials on day 5, *t*(11) = 2.41, p = 0.03. This difference was not due to difference in swimming velocity (p=0.545) or baseline ambulatory velocity (p=0.165).

In summary, we have demonstrated that external beam low-LET X-irradiation produces a significant reduction in amyloid-β plaques, pathologies causatively linked with AD. From our data we cannot determine if the radiation treatment is directly or indirectly eliminating the plaques or alternatively preventing the production and deposition of new amyloid-β plaques. However, these data provide preliminary evidence that these radiation treatments do not negatively affect cognitive function and may even improve some aspects of cognition.

2.0 Objectives and Endpoints

2.1 Primary Objectives

In this proposed study we will assess the safety and toxicity/adverse events associated with the use of low dose fractionated whole brain irradiation in patients who have been diagnosed with probable Alzheimer's disease according to NINCDS-ADRDA criteria.

2.2 Secondary Objectives

1) Investigate whether or not the intervention with low dose whole brain irradiation changes the recognized progression of Alzheimer's disease through cognitive testing.
2) To monitor quality of life parameters.

3) Collect information from AMYViD® PET Scans before and after treatment to investigate if there is any correlation between neurocognitive/quality of life scores and changes in amyloid plaque size, number and location.

2.3 Primary Endpoints

The primary endpoint will be evaluation of toxicity, adverse events and reportable serious adverse events, i.e. grade 3 or higher, as defined by the NCI Common Toxicity Criteria for Adverse Events (CTCAE v. 5.0). RTOG/EORTC Radiation Toxicity Grading is standard of care at Beaumont Hospital for all radiation patients and CTCAE is the standard for reporting & publications. These criteria comprise of various parameters, including performance status, motor function, sensory function, general mental status, nausea/vomiting, hearing loss, xerostomia, and skin toxicity [51]. The CTCAE are cancer-specific and will be supplemented by information from neurocognitive testing using MMSE and ADAS-Cog. The tests will be administered by an appointed, trained site professional at baseline and at 6 weeks, 3 months, 6 months, and 12 months during follow-up. In the context of radiation oncology, the optimal time period for assessing cognitive impairment is within >6 months to 1 year [52,53].

2.4 Secondary Endpoints

1) Neurocognitive testing will be used to assess changes in cognitive function using the MMSE and ADAS-Cog. The tests will be administered by an appointed, trained site professional at baseline and at 6 weeks, 3 months, 6 months, and 12 months during follow-up.
2) Quality of life will be monitored via questionnaires completed by the patient prior to the start of irradiation and at 6 weeks, 3 months, 6 months, and 12 months during follow-up. Specific questionnaires include the QOL-AD and QUALID, which have been established as sensitive measures of various parameters of quality of life.
3) A pretreatment and post treatment (4 months) Amyvid PET/CT scan will be carried out to determine if there are any correlations between neurocognitive /QOL test results and amyloid number, size and location and changes after treatment.

3.0 Methodology

3.1 Dose Levels and Sample Size Calculation

In the context of this pilot study, traditional levels of α (the Type I error rate) and β (the Type II error rate) are inappropriate since the objective of the research is not to provide definitive support for one treatment over another. In trials of safety such as this the objective is to show that the tested intervention produces a safety profile equal to a known standard therapy.

The nearest well-documented clinical situation to this novel study is the use of prophylactic cranial irradiation (PCI) in patients with limited disease small cell lung cancer (SCLC). Between September1999 and December, 2005, 720 patients with limited-stage SCLC in complete remission after chemotherapy and thoracic radiotherapy from 157 centers in 22 countries were randomly assigned to a standard (n=360, 25 Gy in 10 daily fractions of 2.5 Gy) or higher PCI total dose (n=360, 36 Gy) delivered using either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 fractions in 16 days with two daily sessions of

1.5 Gy separated by a minimum interval of 6 hours) radiotherapy [54,55]. In this study 52% of patients experienced acute toxicity during PCI: headache in 85 patients in the 25 Gy group (24%) and 99 patients in the 36 Gy group (28%), respectively, fatigue in 106 (30%) and 121 (34%)

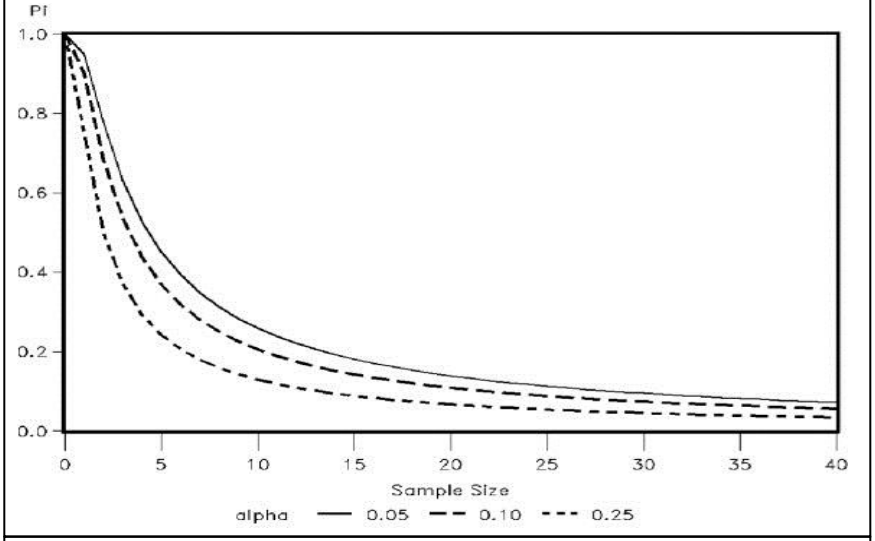

Fig. 2 Upper limit of the 100 × (1 - α)% one-sided confidence interval for the true underlying adverse event rate, π, for increasing sample sizes when zero events of interests are observed

patients, insomnia in 14 (4%) and 13 (4%) patients, and nausea or vomiting in 80 (23%) and 101 patients (28%), with no significant differences between the two groups. Only two patients in the higher-dose group interrupted PCI because of acute toxicity: one because of grade 2 nausea or vomiting, and one because of scalp dermatitis. There were five serious adverse events, all of which occurred in the 25 Gy group: one death (2 months after PCI) with undocumented neurological deterioration, one generalized seizure (12 months after PCI) treated with no sequelae, one transient ischemic attack (6 months after PCI), one bilateral cataract (29 months after PCI), and one death due to generalized seizure in a patient treated for epilepsy (29 days after PCI).

However, at the doses of radiation initially being used in this study (10 Gy) we are unlikely to evoke the common toxicity criteria seen at higher doses. Therefore, we have used the approach of Carter and Woolson [56] whose simple expression has utility for the generation of confidence intervals when zero events are observed. Fig. 2 illustrates, for relatively small sample sizes, there is a large amount of uncertainty. It is critical to convey this uncertainty in the findings and to guard against inferring a potential treatment is harmless when no adverse effects of interest are observed with limited data. Based on this relationship we have chosen an initial cohort of 15 patients to be enrolled in the first treatment scheme (2 Gy x 5 fractions). The first cohort of patients will be followed for 12 months after completion of treatment to assess safety and any toxicity/adverse events associated with treatment. Using this approach, Dr. Coffey (biostatistician) has calculated the upper confidence limits for the event rate when there are 0 events in a group of fifteen distinct patients. The method is consistent with what appears in the classical statistical literature for one-sided confidence limits. Supposing that no events are observed in the results from 15 distinct patients, then the following statements can be made:

- With 99% confidence, the true underlying adverse event rate π does not exceed 26.4%.
- With 95% confidence, the true underlying adverse event rate π does not exceed 18.1%.
- With 90% confidence, the true underlying adverse event rate π does not exceed 14.2%.

The second treatment arm will not be used until the last patient in the first dose arm has completed all follow up. At that point a second cohort of 15 patients will be enrolled in the second dose arm (2 Gy x 10 fractions). The second cohort will undergo a similar stand-alone post-treatment assessment. The starting dose group was chosen as the regimen most commonly used in our pre-clinical studies of AD whilst, the 2 Gy x 10 fractions was chosen as it represents the most commonly used protocol to treat systemic amyloidosis and was the most effective schedule in our preclinical studies of plaque reduction (Table 1) .

As this is a pilot study comprising of two groups of 15 patients, the statistical assessment of endpoints will be descriptive and not inferential. This is a pilot study which is a requisite initial step in exploring an innovative application of radiation treatment and as such its goal is to inform feasibility and identify modifications needed in the design of a larger ensuing hypothesis testing study. In this study we are not testing hypotheses due to the limited state of knowledge about radiation treatment in this population of patients and the FDA-mandated sample size.

3.2 Study Design

This pilot study is a prospective, dose-escalating phase I study that will investigate the safety of low dose external beam radiation of patients with probable moderate stage Alzheimer's Disease. Patients who meet all eligibility requirements and consent to participate in this trial will receive either 10 or 20 Gy delivered in daily 2 Gy fractions using standard whole brain radiotherapy.

3.3 Patient Selection

3.3.1 Recruitment to the study

Patients will be referred from clinicians in the S.E. Michigan area to 2 institutions, Beaumont-Royal Oak and Beaumont-Farmington Hills. If accrual to the study is unsatisfactory, advertisements will be placed after approval of the IRB.

3.3.2 Eligibility Criteria

Patients must meet all eligibility criteria to be included in the study:

1. Must be 55 years of age or older
2. Patient must meet NINCDS-ADRDA criteria for Alzheimer's Disease
3. Patient must be able to complete Mini-Mental Examination and ADAS-Cog Score Sheets
4. Patient has a Rosin Modified Hachinski Ischemic Score of less than or equal to 4
5. Patient has a MMSE score of between 10-20
6. Patient has estimated survival of greater than 12 months
7. Patient or legally authorized representative must be able to give consent

Patients will be excluded from the study if they meet any of the following criteria:

1. The patient has a history of cancer except non-melanoma skin cancer
2. Patient is taking anti-epileptic medication.
3. Dermatological skin disease (lice, ringworm, eczema, or psoriasis) of the scalp.
4. Patient taking Alzheimer medication within the last 3 months, i.e. Exelon, Aricept, Namenda, Reminyl or Epixa.

5. Current presence of a clinically significant major psychiatric disorder (e.g. major depressive disorder, bipolar illness, schizophrenia, etc., according to DSM-IV
6. Patient currently participating in another Clinical Trial.
7. Patient and legally authorized representative unable to give informed consent
8. Patient has history of focal neurological deficits (with the exception of vibratory peripheral neuropathy)
9. Non-Alzheimer dementia
10. Patient has previous history of CNS radiation
11. Patient has evidence of substance abuse (alcohol / or other drugs of dependence) during previous 12 months
12. Patient has history of subdural hygroma / subdural hematoma
13. Patient has history of cerebral infection / hemorrhage
14. Patient has history of being immunocompromised
15. Patient has history of seizure activity
16. Patient has history of hydrocephalus

3.4 Pre-treatment Evaluation and Management

The following tests/evaluations will be completed prior to initiation of treatment:

1) Informed consent: If determined that patient has cognitive impairment which includes decision making capability, a LAR will be used as appropriate for this potentially vulnerable population.
2) Consultation with Co-Investigators(Geriatrics/Neuro Specialists) to assess suitability.
3) The mini-mental state examination (MMSE)
4) The Alzheimer's Disease Assessment Scale2r-Cognitive Subscale (ADAS-Cog)
5) Baseline Quality of life questionnaires (QOL-AD; QUALID)
6) Pre-treatment Amyvid PET/CT Scan
7) Consultation with Radiation Oncologist Investigator prior to enrollment
8) History and Physical

3.5 Pretreatment Evaluation of Cognitive Status

Candidate patients for the study will undergo assessment of general and neurologic history, physical and neurologic examinations and administration of the following psychometric or behavioral tests: the Alzheimer's Disease Assessment Scale2r-Cognitive Subscale (ADAS-Cog) and the mini–mental state examination (MMSE).

The mini–mental state examination (MMSE) and the Alzheimer's Disease Assessment Scale Cognitive scales (ADAS-Cog) have been the most widely used in clinical trials of AD treatments. The MMSE is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used to screen for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document an individual's response to treatment.

Administration of the test takes between 5–10 minutes and examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and

orientation. The ADAS-Cog test is more thorough than the Mini Mental State Exam, and it primarily measures language and memory. The ADAS-Cog consists of 11 parts and takes approximately 30 minutes to administer. It is suggested that a change of 4 or greater in the MMSE is needed before results can be considered different from random events whilst results changes greater than 7 in the ADAS-Cog have been proposed to represent clinically significant changes.

3.6 Pretreatment Amyvid PET/CT Scan

Amyvid (Florbetapir-F18) is a radiopharmaceutical compound approved by the FDA as a diagnostic tool in AD. Amyvid binds to amyloid-β with a half-life of 110 minutes. The tracer significantly accumulates more in brains of patients with AD particularly in the regions known to be associated with amyloid-β deposits [57]. A negative Amyvid scan indicates sparse to no amyloid-β neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid will be administered at a dose of 370 MBq (10 mCi) administered as a single intravenous bolus in a total volume of 10 mL or less. Following the injection, an intravenous flush of 0.9% sterile sodium chloride will be administered. A 10-minute PET image will be acquired starting 30 to 50 minutes after Amyvid intravenous injection. The patient will be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction will include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm. Amyvid images will be interpreted only by the study designated board certified nuclear radiologist. The current guidelines for display and interpretation of Amyvid images will be followed (Appendix VII). Briefly, images will be displayed in the transaxial orientation with access as needed to the sagittal and coronal planes. In reviewing the images, all transaxial slices of the brain will be included using a black-white scale with the maximum intensity of the scale set to the maximum intensity of all the brain pixels. The brain slice with the highest levels of image contrast (highest radioactivity signals for Amyvid uptake) will be located and the contrast adjusted appropriately. Image interpretation will be initiated by displaying slices sequentially from the bottom of the brain to the top. Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of the image assessment. Images are designated as positive or negative by comparing the radioactivity in cortical gray matter with activity in the adjacent white matter.

3.7 Radiation Simulation

Simulation will occur following pretreatment assessments. The patient will be simulated in the supine position, with the shoulders down and the head in neutral position. Non-contrast treatment planning CT will be acquired with the patient in the treatment position. Serial axial images with 2 mm slice thickness will be taken and span the entire head, from at least 5 cm beyond the cranial extent of the skull to the caudal aspect of the seventh cervical vertebral body.

3.8. Low Dose Fractionated Whole Brain Radiation Therapy

3.8.1. Equipment

Treatment will be delivered via a linear accelerator.

3.8.2. Target Volume

The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve, superior to the vertex and posterior to the occiput. The caudal border shall be below the skull base at the top of the C2 vertebral level

3.8.3. Localization

The planning target volume shall be defined by means of a simulator

3.8.4. Dose Prescription and Delivery

The prescription point in the cranial volume is at or near the center. NOTE: regardless of the location of the central axis, the dose should be prescribed at the center on the cranial volume (midway between the maximum separations). The total dose to the prescription point will be 10 Gy for the initial 15 patients then 20 Gy for patients 16-30. This dose will be delivered in 5 fractions or 10 fractions of 2 Gy. All radiation fields shall be treated once each day. The treatment shall be given 5 days a week. No corrections for bone attenuation shall be made. The dose variations in the target volume shall be within +7% (- 5% of the prescription-point dose). No corrections shall be made for treatment interruptions less than 3 days. For interruptions greater than seven days, please contact the site PI.

3.8.5. Treatment Technique

It is recommended that the patient be treated supine. The use of Aquaplast immobilization mask is encouraged but not mandatory. The cranial volume is treated with two lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp. "Compensating beams" that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.Field shaping shall be done with blocks that are at least 5 half-value layers (HVL) thick. Multi-leaf collimation is allowed.

3.9. Radiation On-Treatment Monitoring and Adverse Events

Radiotherapy will be continued without interruption if at all possible as prescribed. If the sum of total radiotherapy interruptions exceeds seven normally scheduled treatment days, the treatment will be considered an unacceptable deviation from the protocol. This patient should

be reported to the principal investigator, and the patient will not be considered for final data analysis. Patients who do not complete a complete, total course of study radiotherapy will be replaced in the study in order to have 15 evaluable patients in each arm.

Patients will be monitored weekly by the treating radiation oncologist for the duration of radiotherapy and at regular intervals following radiotherapy. Scheduled post treatment visits are at 6 weeks 3, 6 and 12 months. At each visit, the patient will undergo an interval history and physical exam and completion of Common Terminology Toxicity Criteria (Version 5.0), and RTOG toxicity scoring to assess any toxicity associated with this study. The RTOG toxicity scoring is done as radiation/oncology standard of care at Beaumont. This will include not only the effects on the CNS but any general adverse effects which may or may not be related to the treatment delivered. Each patient will be assigned a baseline score for skin, eye, ear and CNS and this will be monitored and evaluated during and after treatment for both acute and late toxicity. All adverse events will be recorded on an Adverse Event Reporting Form. The known risks associated with whole brain irradiation at the dose levels described may include, but are not limited to 1) hair loss, 2) decreased hearing, 3) nausea, 4) vomiting and 5) visual changes and 6) skin reactions. The grade or severity of adverse event that is common with the planned radiation dose for this trial based on the RTOG Common Toxicity Criteria are skin (Grade 1), CNS (Grade 1), ocular (Grade 0) and brain (Grade 1). All related/possibly related Grade ≥ 3 Toxicities will be reported as unexpected in severity to the IRB and monthly to the DSMB.

If at any time during the study there is an increase of 2 or more points, an evaluation by the DSMB will take place within the week to determine if it is therapy related or due to other non-study related events. Should this happen during the course of the treatment, therapy will be immediately stopped and all medical attempts will be made to correct the cause of the noted decline. The records and information related to the event will be reported to the IRB and the FDA using standard reporting mechanism. If it is determined that the toxicity was not study related accrual will resume once cleared by IRB.

Supportive management of symptoms (e.g., the use of oral or intravenous steroids for brain edema and the use of antiemetics) is permitted at the discretion of the treating radiation oncologist, neurologist or neurosurgeon.

3.10. Cognitive Assessment and Quality of Life Assessment During Treatment

The Mini Mental Exam and ADAS-Cog are the two most commonly used tests of cognition in Alzheimer's Disease [58]. After treatment these tests will be administered by study designated, trained professional at 6 (+1) weeks, 3 (+1) months, 6 (+1) months and 12 months. Given that the ADAS-Cog is not used routinely in clinical practice (but rather a research assessment) and that the personnel involved may not necessarily be doing other studies requiring ADAS-Cog, it will not be possible to blind the professional doing the testing. The ADAS-Cog yields a single score that reflects the arbitrary weighting of performance in several cognitive domains including learning, language and spatial cognition but does not address executive function. A normal score for someone who does not have Alzheimer's or another type of dementia is 5; the greater

the dysfunction, the greater the score [59]. The properties of the ADAS-Cog are well understood; there is a curvilinear relationship between disease severity and rate of change on the ADAS-Cog. In a large clinical trial the baseline score for placebo-treated patients in the ADAS-Cog range of 13 to 26 was 24.2 ± 9.4 and this increased to 29.9 ± 13.7 representing a decline of 5.7 ± 8.2 points over 1 year [60]. In this trial, a significant benefit in the active group was considered to be a 50% reduction in cognitive decline as indicated by change in ADAS- Cog score compared with the placebo group. In this study, patients who have an increase of no more than 50% (~3 points) on the ADAS-Cog at the end of treatment will be considered responders. This is equivalent to a delay in decline of about 6-8 months. Longitudinal analysis will be carried out for each individual patient using a fixed quadratic effect of time, dependent on the baseline level of ADAS-Cog, i.e., an interaction of baseline ADAS-Cog and the quadratic component of time.

The MMSE is a commonly used 30-point scale for assessing cognitive function in the domains of orientation, registration, attention and calculation, recall, language, and praxis. A MMSE score of 10 to 20 suggests moderate dementia. On average, the MMSE score of a person with moderate dementia declines about three to four points in a 12-month period. A similar analysis to that described above for the ADAS-Cog test will be carried out taking into account time and baseline MMSE score.

Completion of Quality of Life indices (Quality of Life-AD and QUALID Scale) analysis will be completed by PI designated research staffat the same visit for cognitive testing.

3.11 Post-treatment Amyvid PET/CT Scan

A second Amyvid (Florbetapir-F18) PET scan will be done at 4 months after completion of treatment. Amyvid will be administered at a dose of 370 MBq (10 mCi) administered as a single intravenous bolus in a total volume of 10 mL or less. Following the injection, an intravenous flush of 0.9% sterile sodium chloride will be administered. A 10-minute PET image will be acquired starting 30 to 50 minutes after Amyvid intravenous injection. The patient will be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction will include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm. Amyvid images will be interpreted only by the study designated nuclear radiologist. Analysis will be carried out as previously described.Pre- and post-radiation scans will be presented in random order, with the nuclear radiologist blinded to the order of presentation and patient identity or clinical details

3.12 Stopping Rules

This study will be stopped for any of the following reasons

1) Any patient death attributed totreatment
2) Any patient who develops a Grade IV adverse event
3) More than 3 of 15 patients who develop a Grade 3 adverse event as per CTCAE v.5.0 in either group
4) 50% or more patients in either group have no change or increase in amyloid based on Amyvid PET Scan

5) 5 patients that show greater than 4 point deterioration in MMSE in two consecutive cognition evaluations
6) 5 patients that show increases greater than 7 on ADAS-Cog scale.

4.0 Risks and Benefits

Patients will be advised that the use of radiation to treat Alzheimer's disease has not been reported and such treatment should be considered investigational. There is the possibility that treatment-related adverse events may be observed. Close monitoring with frequent assessment of toxicity and signs of progression will be performed and reported. There is the possibility that radiation treatment may improve cognitive decline resulting in benefit for the patient.

5.0 Data Safety Monitoring Plan

The appointed Data Safety and Monitoring Board (DSMB) will act in an advisory capacity to the IDE Sponsor/Investigator and the Beaumont Research Institute to monitor participant safety, data quality and evaluate the progress of the study.

The DSMB will consist of four members (three voting, one non-voting) who are not directly involved in the trial and have expertise in the fields of radiation and/or Alzheimer's disease management, clinical trial methodology, and/or biostatistics. Prior to implementation of the protocol, the DSMB will meet to review the protocol and informed consent documents, approve templates for study summary reports, and to adopt the charter.

The DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. Meetings of the DSMB may occur as frequently as monthly during the enrollment and treatment phase of the trial. Monthly meetings will be scheduled, however, prior to each meeting, the DSMB Chair will review the agenda. If there are no new enrollments, additional study data, or updates from the IDE Sponsor/Investigator, the DSMB Chair may cancel the meeting.

After enrollment has stopped, the DSMB will meet quarterly. The DSMB will discharge itself from its duties when the last participant completes the study.

The DSMB Chair will provide a written report after each meeting containing DSMB recommendations as to whether the study should continue without change, be modified, or terminated. The DSMB Chair will provide the written report to the IDE Sponsor/Investigator and the Beaumont Research Institute. The IDE Sponsor/Investigator will submit the report to the Site Investigator(s) and the FDA. The Site Investigator(s) will submit the reports to their respective IRBs.

Along with meeting at regular intervals during the conduct of the trial, the DSMB will meet within one week of any adverse event that increases by 2 or more points according to the

Common Terminology Toxicity Criteria and RTOG toxicity scoring. The DSMB will meet to determine if the adverse event is related to therapy or due to other non-study related events. Following the meeting, the DSMB Chair will provide the DSMB determination in writing to the IDE Sponsor/Investigator and the Beaumont Research Institute. The IDE Sponsor/Investigator will submit the determination to the FDA, if required, and the Site Investigator(s). The Site Investigator(s) will submit the DSMB determination to their respective IRBs.

The DSMB will consist of the following individuals:

- Paul Chuba, MD, Medical Director of Radiation Oncology, St. John Hospital and Medical Center, Detroit, MI
- Martin Hauer-Jensen, MD, PhD, Director of Radiation Biology Research, University of Arkansas for Medical Science, Little Rock, AR
- H. Michael Yu, MD, Professor of Radiation Oncology, CNS Service Chief, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
- Robert Podolsky, PhD, Director of Informatics and Biostatistics, Beaumont Research Institute, Royal Oak, MI (non-voting member)

6.0 Study Calendar

	Pre Treatment	Daily Radiation Treatment	6 Weeks Post Treatment +/- 1 week	Post Treatment (Months)			
				3 +/- 2 weeks	4 +/- 2 weeks	6 +/- 2 weeks	12 +/- 2 weeks
ADAS-Cog	X		X	X		X	X
MMSE	X		X	X		X	X
History & Physical	X		X	X		X	X
AMYViD PET scan	X				X		
Toxicity Evaluation	X	X	X	X		X	X
QOL-AD and QUALID	X		X	X		X	X

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Appendix I: Eligibility Checklist

Patient No:_____Patient Name:_____

Inclusion Criteria for Eligibility (All responses must be **Yes**)

Yes No

_____ _____ 1. Patient is 55 years of age or older

_____ _____ 2. Patient meets NINCDS-ADRDA criteria for Alzheimer's Disease

_____ _____ 3. Patient must be able to complete Mini-Mental Examination and ADAS-Cog Score Sheets

_____ _____ 4. Patient has a Rosin Modified Hachinski Ischemic Score of less than or equal to 4

_____ _____ 5. Patient has a MMSE score of between 10-20

_____ _____ 6. Patients has estimated survival of greater than 12 months

_____ _____ 7. Patient or legally authorized representative is able to give consent

_____ _____

Investigator Signature Date

Exclusion Criteria for Eligibility (All responses must be **No**)

Yes No

_____ _____ 1. Patient has a history of cancer except non-melanoma skin cancer
_____ _____ 2. Patient is taking anti-epileptic medication.
_____ _____ 3. Patient has dermatological skin disease (lice, ringworm, eczema, or psoriasis) of the scalp
_____ _____ 4. Patient is taking Alzheimer medication within the last 3 months, i.e. Exelon, Aricept, Namenda, Reminyl or Epixa.
_____ _____ 5. Patient has current presence of a clinically significant major psychiatric disorder (e.g. major depressive disorder, bipolar illness, schizophrenia, etc., according to DSM-IV)
_____ _____ 6. Patient is currently participating in another Clinical Trial.
_____ _____ 7. Patient and legally authorized representative are unable to give informed consent
_____ _____ 8. Patient has history of focal neurological deficits (with the exception of vibratory peripheral neuropathy)
_____ _____ 9. Patient has non-Alzheimer dementia
_____ _____ 10. Patient has previous history of CNS radiation
_____ _____ 11. Patient has evidence of substance abuse (alcohol / or other drugs of dependence) during the previous 12 months
_____ _____ 12. Patient has history of subdural hygroma / subdural hematoma
_____ _____ 13. Patient has history of cerebral infection / hemorrhage
_____ _____ 14. Patient has history of being immunocompromised
_____ _____ 15. Patient has history of seizure activity
_____ _____ 16. Patient has history of hydrocephalus

_____ _____
Investigator Signature Date

Appendix II: NINCDS-ADRDA Score

https://www.alzheimersanddementia.com/article/S1552-5260(11)00101-4/fulltext

Appendix III: CTCAE V.5.0 criteria for assessment of anticipated toxicity

ALZHEIMER DISEASE RT STUDY TOXICITY WORKSHEET

Date_____

ID#_____**Name**_____**MD**_____

Physician Signature:_____ **Date/Time:** _____ ___

Skin Toxicity:
Radiation recall reaction (dermatologic)
☐ Grade 0, None
☐ Grade 1, Faint erythema or dry desquamation
☐ Grade 2, Moderate to brisk erythema; patchy moist desquamation mostly confined to skin folds and creases; moderate edema
☐ Grade 3, Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasions
☐ Grade 4, Life threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Alopecia
☐ Grade 0, None
☐ Grade 1, Hair loss <50% normal for that individual; not obvious from distance but only on close inspection
☐ Grade 2, Hair loss >50%; wig/hair piece need if patient desires to completely camouflage hair loss associated with psychosocial impact
Xerostomia
☐ Grade 0, None
☐ Grade 1, Symptomatic (dry or thick saliva) without significant dietary alteration, unstimulated saliva flow > 0.2 ml/minute
☐ Grade 2, Moderate symptoms, oral intake alteration (copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva elow 0.1-0.2 ml/minute
☐ Grade 3, Inability to adequately aliment orally (IV fluids, tube feedings, or TPN indicated), unstimulated saliva flow < 0.1 ml/minute

☐ **Other skin toxicity not listed above**_____

Eye Toxicity:
Blurred Vision
☐ Grade 0, None
☐ Grade 1, Intervention not indicated
☐ Grade 2, Symptomatic; limiting instrumental ADL
☐ Grade 3, Limiting self care ADL
Cataract
☐ Grade 0, None
☐ Grade 1, Asymptomatic; intervention not indicated
☐ Grade 2, Symptomatic; moderate decrease in visual acuity (20/40 or better)
☐ Grade 3, Symptomatic with marked decrease in visual acuity-operative intervention indicated
☐ Grade 4, Blindness (20/200 or worse) in affected eye

☐ **Other eye toxicity not listed above**_____

Ear Toxicity:
Ear Pain (Definition: a disorder characterized by a sensation of marked discomfort inside the ear)
☐ Grade 0, None
☐ Grade 1, Mild pain
☐ Grade 2, Moderate pain; limiting instrumental ADL
☐ Grade 3, Severe pain; limiting self care ADL
Hearing Loss
☐ Grade 0, None
☐ Grade 1, Subjective change in hearing in the absence of documented hearing loss
☐ Grade 2, Hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.
☐ Grade 3, Hearing loss with hearing aid or intervention indicated
☐ Grade 4, Decrease in hearing to profound bilateral loss; non-servicable hearing.
Additional hearing loss since treatment ☐ No ☐ Yes

☐ **Other ear toxicity not listed above**_____

CNS Toxicity:
Fatigue
☐ Grade 0, None
☐ Grade 1, Fatigue relieved by rest
☐ Grade 2, Fatigue not relieved by rest; limiting instrumental ADL
☐ Grade 3, Fatigue not relieved by rest, limiting self care ADL
Neuropathy (Motor)
☐ Grade 0, None
☐ Grade 1, Asymptomatic, clinical or diagnostic observations only; intervention not indicated
☐ Grade 2, Moderate symptoms; limiting instrumental ADL
☐ Grade 3, Severe symptoms; limiting self care ADL; assistive device indicated
☐ Grade 4, Life threatening consequences; urgent intervention indicated
Neuropathy (Sensory)
☐ Grade 0, None
☐ Grade 1, Asymptomatic, loss of deep tendon reflexes or paresthesia
☐ Grade 2, Moderate symptoms; limiting instrumental ADL
☐ Grade 3, Severe symptoms; limiting self care ADL
☐ Grade 4, Life threatening consequences; urgent intervention indicated
Nausea
☐ Grade 0, None
☐ Grade 1, Loss of appetite without alteration in eating habits
☐ Grade 2, Oral intake decreased without significant weight loss, dehydration or malnutrition
☐ Grade 3, Inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated
Vomiting
☐ Grade 0, None
☐ Grade 1, 1-2 episodes, separated by 5 minutes, in 24 hours
☐ Grade 2, 3-5 episodes, separated by 5 minutes, in 24 hours
☐ Grade 3, ≥ 6 episodes, separated by 5 minutes, in 24 hrs; tube feeding, TPN or hospitalization indicated
☐ Grade 4, Life threatening consequences; urgent intervention indicated

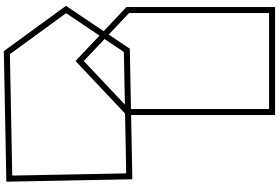
☐ **Other CNS toxicity not listed above**_____

IRB NUMBER: 2017-471
IRB APPROVAL DATE: 01/09/2020

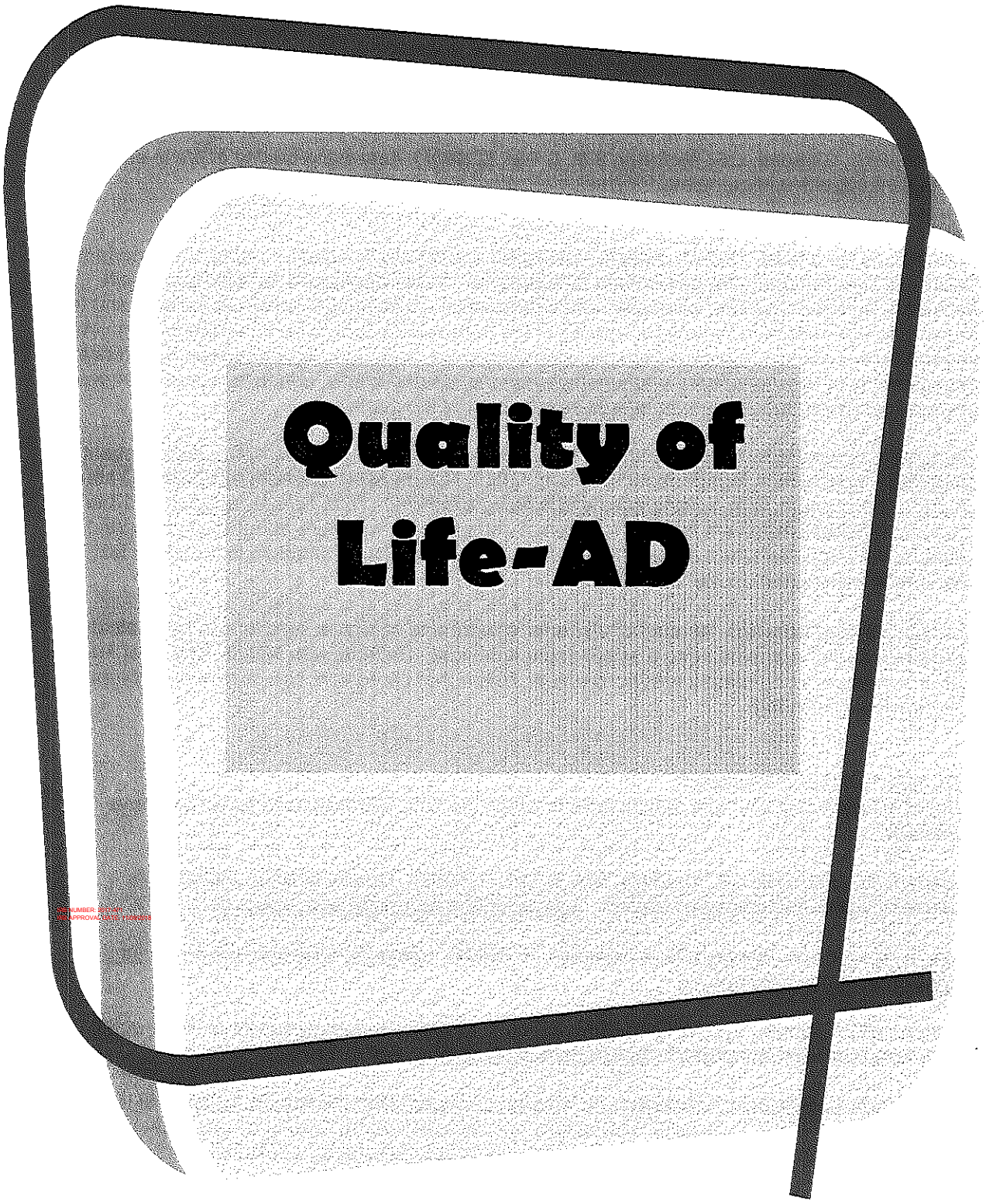
Name: Date

Mental Status (Folstein Scale)

			Item	Score
Orientation	1-5	What is today's date?	1. Date 2. Year 3. Month 4. Day 5. Season	_____ _____ _____ _____ _____
	6-10	Can you tell me the name of the place where we are today? What floor are we on? What town are we in? What County are we in? What State are we in?	6. Institution 7. Floor 8. Town 9. County 10. State	_____ _____ _____ _____ _____
Registration	11-13	Ask if you may test memory. Use 3 objects: ball, flag, & tree. State them slowly and clearly. Ask for them to be repeated. The first repetition determines the score (0-3), but continue until repeated correctly (maximum 6 tries)	11. Ball 12. Flag 13. Tree	_____ _____ _____
Attention and Calculation	14-18	Begin with 100 and count backwards by 7. Stop after 5 subtractions (65). Score the total number of correct answers. If the subject cannot perform this, ask him/her to spell "world" backwards, scoring the number of letters in correct order.	14. 93 15. 86 16. 79 17. 72 18. 65 or dlrow	_____ _____ _____ _____ _____ _____
Recall	19-21	"Now recall the 3 words I asked you to remember"	19. Ball 20. Flag 21. Tree	_____ _____ _____
Language	22-23	Naming: Show and ask the names of **wristwatch, pencil**	22. Watch 23. Pencil	_____ _____
	24	Repetition: no ifs, ands or buts"	24. Repetition	_____
	25-27	3-stage command: Give the subject a blank sheet of paper and say "take the paper in your right hand, fold it in half and place on the floor".	25. Takes 26. Folds 27. Places	_____ _____ _____
	28	Reading: Print **"close your eyes"** in large letters and instruct subject to "Do what this says".	28. Reading	_____
	29	Spontaneous writing: Ask the subject to write a sentence on a sheet of paper. It should be a sensible sentence with a subject and verb	29. Sentence	_____
	30.	Coping: Draw this figure – all 10 angles must be present with 2 intersects to score one point.	30. Draws pentagons	_____



TOTAL SCORE:



Brief Descriptive Information about the Quality of Life-AD Measure

References:

Logsdon, R.G., Gibbons, L.E., McCurry, S.M., & Teri, L. (1999). Quality of life in Alzheimer's disease: Patient and caregiver reports. *Journal of Mental Health & Aging*, Volume *5*, Number 1, pages 21-32.

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Description:

The QOL-AD is a brief, 13-item measure designed specifically to obtain a rating of the patient's Quality of Life from both the patient and the caregiver. It was developed for individuals with dementia, based on patient, caregiver, and expert input, to maximize construct validity, and to ensure that the measure focuses on quality of life domains thought to be important in cognitively impaired older adults. It uses simple and straightforward language and responses & includes assessments of the individual's relationships with friends and family, concerns about finances, physical condition, mood, and an overall assessment of life quality.

Caregivers complete the measure as a questionnaire about their patients' QOL, while patients complete it in interview format about their own QOL. The measure consists of 13 items, rated on a four point scale, with 1 being poor and 4 being excellent. Total scores range from 13 to 52. It generally takes caregivers about 5 minutes to complete the measure about their patients; for patients, the interview takes about 10 to 15 minutes to administer. Detailed instructions for interviewer administration are available.

Scoring is straightforward- the sum of all items; patient and caregiver reports can be evaluated separately and/or combined into a single score if desired. Patients with MMSE scores of 10 or higher can usually complete it with no problem; below that caregivers can continue to complete it as proxies indefinitely.

QOL-AD Published Research

(studies marked with an * are clinical trials in which the QOL-AD was used as an outcome measure)

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Quality of Life: AD

(Interview Version for the person with dementia)

Interviewer administer according to standard instructions.
Circle responses.

1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments:_____

Quality of Life-AD
Instructions for Interviewers

The QOL-AD is administered in interview format to individuals with dementia, following the instructions below. Hand the form to the participant, so that he or she may look at it as you give the following instructions (instructions should closely follow the wording given in bold type):

I want to ask you some questions about your quality of life and have you rate different aspects of your life using one of four words: poor, fair, good, or excellent.

Point to each word (poor, fair, good, and excellent) on the form as you say it.

When you think about your life, there are different aspects, like your physical health, energy, family, money, and others. I'm going to ask you to rate each of these areas. We want to find out how you feel about your current situation in each area.

If you're not sure about what a question means, you can ask me about it. If you have difficulty rating any item, just give it your best guess.

It is usually apparent whether an individual understands the questions, and most individuals who are able to communicate and respond to simple questions can understand the measure. If the participant answers all questions the same, or says something that indicates a lack of understanding, the interviewer is encouraged to clarify the question. However, under no circumstances should the interviewer suggest a specific response. Each of the four possible responses should be presented, and the participant should pick one of the four.

If a participant is unable to choose a response to a particular item or items, this should be noted in the comments. If the participant is unable to comprehend and/or respond to two or more items, the testing may be discontinued, and this should be noted in the comments.

As you read the items listed below, ask the participant to circle her/his response. If the participant has difficulty circling the word, you may ask her/him to point to the word or say the word, and you may circle it for him or her. You should let the participant hold his or her own copy of the measure, and follow along as you read each item.

1. **First of all, how do you feel about your physical health? Would you say it's poor, fair, good, or excellent? Circle whichever word you think best describes your physical health right now.**

2. **How do you feel about your energy level? Do you think it is poor, fair, good, or excellent?** If the participant says that some days are better than others, ask him or her to rate how she/he has been feeling most of the time lately.

3. **How has your mood been lately? Have your spirits been good, or have you been feeling down? Would you rate your mood as poor, fair, good, or excellent?**
4. **How about your living situation? How do you feel about the place you live now? Would you say it's poor, fair, good, or excellent?**

5. **How about your memory? Would you say it is poor, fair, good, or excellent?**

6. **How about your family and your relationship with family members? Would you describe it as poor, fair, good, or excellent?** If the respondent says they have no family, ask about brothers, sisters, children, nieces, nephews.

7. **How do you feel about your marriage? How is your relationship with (spouse's name). Do you feel it's poor, fair, good, or excellent?** Some participants will be single, widowed, or divorced. When this is the case, ask how they feel about the person with whom they have the closest relationship, whether it's a family member or friend. If there is a family caregiver, ask about their relationship with this person. It there is no one appropriate, or the participant is unsure, score the item as missing. If the participant's rating is of their relationship with someone other than their spouse, note this and record the relationship in the comments section.

8. **How would you describe your current relationship with your friends? Would you say it's poor, fair, good, or excellent?** If the respondent answers that they have no friends, or all their friends have died, probe further. **Do you have anyone you enjoy being with besides your family? Would you call that person a friend?** If the respondent still says they have no friends, ask **how do you feel about having no friends—poor, fair, good, or excellent?**

9. **How do you feel about yourself—when you think of your whole self, and all the different things about you, would you say it's poor, fair, good, or excellent?**

10. **How do you feel about your ability to do things like chores around the house or other things you need to do? Would you say it's poor, fair, good, or excellent?**

11. **How about your ability to do things for fun, that you enjoy? Would you say it's poor, fair, good, or excellent?**

12. **How do you feel about your current situation with money, your financial situation? Do you feel it's poor, fair, good, or excellent?** If the respondent hesitates, explain that you don't want to know what their situation is (as in amount of money), just how they feel about it.

13. **How would you describe your life as a whole. When you think about your life as a whole, everything together, how do you feel about your life? Would you say it's poor, fair, good, or excellent?**

SCORING INSTRUCTIONS FOR THE QOL:

Points are assigned to each item as follows: poor=1, fair=2, good=3, excellent=4.
The total score is the sum of all 13 items.

Quality of Life: AD

(Questionnaire Version for the Family Member or Caregiver)

The following questions are about your relative's quality of life.

When you think about your relative's life, there are different aspects, some of which are listed below. Please think about each item, and rate your relative's current quality of life in each area using one of four words: **poor, fair, good, or excellent**. Please rate these items based on your relative's life **at the present time** (e.g. within the past few weeks). If you have questions about any item, please ask the person who gave you this form for assistance.

Circle your responses.

1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments:_____

_____

APPENDIX VI

QUALID SCALE

QUALITY OF LIFE IN Llate-STAGE DEMENTIA (QUALID) SCALE ©

Name (L, F, MI)	Date (M/D/Y)
_____	_____/_____/_____

The QUALID is administered in interview format to an informant following the instructions below.

Informants may be either a family member or professional caregiver who by having regular contact is familiar with the subject's general behavior. Informants must, in addition to being familiar with the subject, have spent a significant portion of at least 3 days out of the last 7 days with the subject, in order to accurately rate the items on the scale. The scale is scored by summing the responses. The possible scores range from 11 to 55, with 11 representing the highest quality of life

The final items on the scale require that the interviewer make a judgement about the validity of the interview. Provide both a rating of the overall quality of the interview, which includes the informant's ability to understand the items and responses and the effort the informant put forth in answering questions, and the familiarity of the informant with the subject. These items are not included in the score, but offer information about the validity and usefulness of the ratings for that subject.

Informants are handed a blank copy of the scale so that they may look at the items as they are read aloud, and the following instructions are given:

> **I want to ask you some questions about** *name's* **quality of life. I want you to rate his/her behaviors using the responses under each question on this page.** (*point to the responses on the first question)* **There is no one right or wrong answer, I just want to know how you would rate his/her behavior from your observations.**
>
> **Specifically, I want to know about his/her behavior over the past week only, not how he/she previously behaved. Remember that your answers should reflect his/her behavior over the past seven days. If you are not sure what the question means, you can ask me about it. If you have difficulty choosing a rating for an item, just make your best guess. Again, indicate your observation about his/her behavior over the past week.**

Which response best describes _____ over the past week…

A. [S] smiles
1. spontaneously once or more each day
2. spontaneously less than once each day
3. only in response to external stimuli; at least once each day
4. only in response to external stimuli; less than once each day
5. rarely, if at all

B. [S] appears sad
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. for no apparent reason less than once each day
5. for no apparent reason once or more each day

C. [S] cries
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. for no apparent reason less than once each day
5. for no apparent reason once each day or more

QUALITY OF LIFE IN LATE-STAGE DEMENTIA (QUALID) SCALE ©

_____	_____/_____/_____
Name (L, F, MI)	Date (M/D/Y)

D. [S] has a facial expression of discomfort - appears unhappy or in pain (looks worried, grimaces, furrowed or turned down brow)
1. rarely or never
2. less than once each day
3. at least once each day
4. nearly half of each day
5. most of each day

E. [S] appears physically uncomfortable –he/she squirms, writhes, frequently changes position
1. rarely or never
2. less than once each day
3. at least once each day
4. nearly half of each day
5. most of each day

F. [S] makes statements or sounds that suggest discontent, unhappiness or discomfort (complains, groans, screams)
1. rarely or never
2. only in response to external stimuli; less than once each
3. only in response to external stimuli; at least once each day
4. without cause less than once each day
5. without cause once or more each day

G. [S] is irritable or aggressive (becomes angry, curses, pushes or attempts to hurt others)
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. without cause less than once each day
5. without cause once or more each day

H. [S] enjoys eating
1. at most meals and snacks
2. twice a day
3. at least once a day
4. less than once each day
5. rarely or never

I. [S] enjoys touching/being touched
1. almost always; almost always initiates touching
2. more than half the time; sometimes initiates touching
3. half the time; never initiates touching, but doesn't resist touching
4. less than half the time; often or frequently resists touching/being touched
5. rarely or never; almost always resists touching/being touched

QUALITY OF LIFE IN LATE-STAGE DEMENTIA (QUALID) SCALE ©

Name (L, F, MI)	Date (M/D/Y)
_____	_____/_____/_____

J. [S] enjoys interacting or being with others
1. almost always; almost always initiates interaction with others
2. more than half the time; sometimes initiates interaction with others
3. half the time; never initiates interaction, but doesn't resist interaction with others
4. less than half the time; often or frequently resists interacting with others
5. rarely or never; almost always resists interacting with others

K. [S] appears emotionally calm and comfortable
1. most of each day
2. more than half of each day
3. half of each day
4. less than half of each day
5. rarely or never

_____Total Score (sum of all items; scores range from 11 to 55 with lower scores representing higher quality of life)

Quality of Interview (Administrator's judgement):
0 Interview appeared valid
1 Some questions about interview, but probably acceptable
2 Information from interview of doubtful validity

Knowledge/familiarity of caregiver with subject:
0 Very familiar; provides daily care
1 Somewhat familiar; often provides some care
2 Not very familiar; only dispenses meds, minimal contact

Weiner, M.F., Martin-Cook, K., Svetlik, D.A., Saine, K., Foster, B., & Fontaine, C. The quality of life in late-stage dementia (QUALID) scale. *J Am Med Dir Assn*, 2000;1:114-116

Which response best describes _____ over the past week…

A. [S] smiles
1. spontaneously once or more each day
2. spontaneously less than once each day
3. only in response to external stimuli; at least once each day
4. only in response to external stimuli; less than once each day
5. rarely, if at all

B. [S] appears sad
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. for no apparent reason less than once each day
5. for no apparent reason once or more each day

C. [S] cries
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. for no apparent reason less than once each day
5. for no apparent reason once each day or more

D. [S] has a facial expression of discomfort - appears unhappy or in pain (looks worried, grimaces, furrowed or turned down brow)
1. rarely or never
2. less than once each day
3. at least once each day
4. nearly half of each day
5. most of each day

E. [S] appears physically uncomfortable –he/she squirms, writhes, frequently changes position
1. rarely or never
2. less than once each day
3. at least once each day
4. nearly half of each day
5. most of each day

F. [S] makes statements or sounds that suggest discontent, unhappiness or discomfort (complains, groans, screams)

1. rarely or never
2. only in response to external stimuli; less than once each
3. only in response to external stimuli; at least once each day
4. without cause less than once each day
5. without cause once or more each day

G. [S] is irritable or aggressive (becomes angry, curses, pushes or attempts to hurt others)
1. rarely or never
2. only in response to external stimuli; less than once each day
3. only in response to external stimuli; at least once each day
4. without cause less than once each day
5. without cause once or more each day

H. [S] enjoys eating
1. at most meals and snacks
2. twice a day
3. at least once a day
4. less than once each day
5. rarely or never

I. [S] enjoys touching/being touched
1. almost always; almost always initiates touching
2. more than half the time; sometimes initiates touching
3. half the time; never initiates touching, but doesn't resist touching
4. less than half the time; often or frequently resists touching/being touched
5. rarely or never; almost always resists touching/being touched

J. [S] enjoys interacting or being with others
1. almost always; almost always initiates interaction with others
2. more than half the time; sometimes initiates interaction with others
3. half the time; never initiates interaction, but doesn't resist interaction with others
4. less than half the time; often or frequently resists interacting with others
5. rarely or never; almost always resists interacting with others

K. [S] appears emotionally calm and comfortable
1. most of each day
2. more than half of each day
3. half of each day
4. less than half of each day
5. rarely or never

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Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior

SAMPLE FORM – Page 1 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

1. WORD RECALL TASK: Indicate the total number of ***correct*** responses for each trial

Trial 1	Trial 2	Trial 3

2. NAMING OBJECTS AND FINGERS: Check each object/finger named ***correctly*** or check "NONE."

NONE ☐

☐ Flower	☐ Rattle	☐ Wallet
☐ Bed	☐ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
☐ Pencil	☐ Comb	☐ Tongs
☐ Thumb	☐ Index	☐ Ring
☐ Pinky	☐ Middle	

3. COMMANDS: Check each command performed ***correctly*** or check "NONE." NONE ☐

- ☐ Make a fist.
- ☐ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ☐ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn ***correctly***.

- ☐ None: attempted but drew no forms correctly.
- ☐ Patient drew no forms; scribbled; wrote words.
- ☐ Circle
- ☐ Two overlapping rectangles
- ☐ Rhombus
- ☐ Cube

5. IDEATIONAL PRAXIS: Check each step completed ***correctly*** *or* check "NONE" NONE ☐

- ☐ Fold a letter.
- ☐ Put letter in envelope.
- ☐ Seal envelope.
- ☐ Address envelope.
- ☐ Indicate where stamp goes.

6. ORIENTATION: Check each item answered ***correctly*** or check "NONE." NONE ☐

☐ Full name	☐ Day
☐ Month	☐ Season
☐ Date	☐ Place
☐ Year	☐ Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

Trial 1	Trial 2	Trial 3
X	X	X

8. LANGUAGE: Check level of impairment.

- ☐ **None**: patient speaks clearly and/or is understandable.
- ☐ **Very Mild**: one instance of lack of understandability.
- ☐ **Mild**: patient has difficulty < 25% of the time.
- ☐ **Moderate**: patient has difficulty 25–50% of the time.
- ☐ **Moderately Severe**: patient has difficulty more than 50% of the time.
- ☐ **Severe**: one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

- ☐ **None**: patient understands.
- ☐ **Very Mild**: one instance of misunderstanding.
- ☐ **Mild**: 3–5 instances of misunderstanding.
- ☐ **Moderate**: requires several repetitions and rephrasing.
- ☐ **Moderately Severe**: patient only occasionally responds correctly; i.e., yes – no questions.
- ☐ **Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

- ☐ **None.**
- ☐ **Very Mild**: 1 or 2 instances, not clinically significant.
- ☐ **Mild**: noticeable circumlocution or synonym substitution.
- ☐ **Moderate**: loss of words without compensation on occasion.
- ☐ **Moderately Severe**: frequent loss of words without compensation.
- ☐ **Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

- ☐ **None.**
- ☐ **Very Mild**: forgets once.
- ☐ **Mild**: must be reminded 2 times.
- ☐ **Moderate**: must be reminded 3–4 times.
- ☐ **Moderately Severe**: must be reminded 5–6 times
- ☐ **Severe**: must be reminded 7 or more times.

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Alzheimer's Disease Cooperative Study

ADAS – Word Recall

SAMPLE FORM – Page 2 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - -			Month Day Year

Present Word List #2.

Check EACH word correctly recalled.

TRIAL 1		TRIAL 2		TRIAL 3	
BOTTLE		FOREST		GIRL	
POTATO		TEMPLE		TEMPLE	
GIRL		BOTTLE		POTATO	
TEMPLE		STAR		ANIMAL	
STAR		POTATO		FOREST	
ANIMAL		GIRL		LAKE	
FOREST		CLOCK		OFFICE	
LAKE		ANIMAL		CLOCK	
CLOCK		LAKE		BOTTLE	
OFFICE		OFFICE		STAR	
TOTAL		**TOTAL**		**TOTAL**	

Indicate total number of words correctly recalled for EACH trial on the ADAS Cognitive Behavior Form.

12. Executive Function (Maze):

a. ☐☐ number of errors

b. ☐☐ time at completion or second error (total seconds)

13. Number Cancellation:

a. ☐☐ number of targets hit (Range: 0 - 40)

b. ☐☐ number of errors

c. ☐☐ number of times to remind of task

If any item(s) 1-13 are incomplete or not done, please specify reason:

☐ Subject too cognitively impaired to complete

☐ Subject was unable to complete for physical reasons

☐ Subject refused

☐ Not Done, for reason other than above explain: _____

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Alzheimer's Disease Cooperative Study

ADAS – Delayed Recall

SAMPLE FORM – Page 3 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - -			Month Day Year

Instructions: Say to the patient, **"NOW I WANT YOU TO TRY TO REMEMBER THE WORDS THAT I SHOWED YOU EARLIER ON PRINTED CARDS. CAN YOU TELL ME ANY OF THOSE WORDS?"**

Allow a maximum of two minutes for recall.

check EACH word correctly recalled.

BOTTLE	
POTATO	
GIRL	
TEMPLE	
STAR	
ANIMAL	
FOREST	
LAKE	
CLOCK	
OFFICE	
TOTAL	

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Alzheimer's Disease Cooperative Study

ADAS – Word Recognition

SAMPLE FORM – Page 4 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R - -			Month Day Year

Present Word List #2.

Check subject's response for each word. Subject should respond "yes" to original words which are bolded. INCORRECT responses are shaded. Three trials of reading and recognition are given.

	Yes	No
COST		
NATION		
CHIMNEY		
SPARROW		
DAMAGES		
TRAFFIC		
SANDWICH		
SERVICE		
SHELL		
SOLUTION		
YARD		
TUBE		
BODY		
GROUND		
STICK		
ENGINE		
RICHES		
GRAVITY		
SUMMER		
WISDOM		
MAN		
MEAL		
PASSENGER		
ACID		

	Yes	No
BATTLE		
MUCH		
TUBE		
TEAM		
COPY		
ENGINE		
GRAVITY		
COST		
JAR		
DISTANCE		
TRIUMPH		
TEMPER		
SENTENCE		
FOX		
PASSENGER		
SANDWICH		
SOLUTION		
WHISTLE		
CHIMNEY		
UNION		
ACID		
MEAL		
DAMAGES		
RICHES		

	Yes	No
VISITOR		
ACID		
SPEAK		
SOLUTION		
NAME		
MEAL		
LINE		
BILL		
CHIMNEY		
ENGINE		
WEALTH		
TUBE		
IMAGE		
COST		
SANDWICH		
DAMAGES		
ELEPHANT		
RICHES		
GRAVITY		
FUTURE		
PASSENGER		
STRING		
BANNER		
BERRY		

*see procedures manual for further clarification

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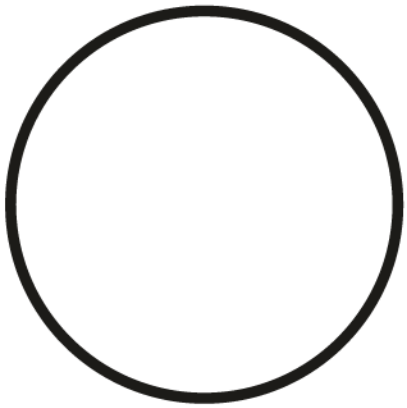

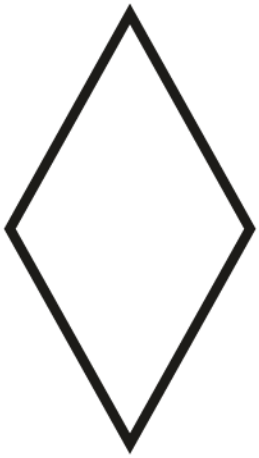

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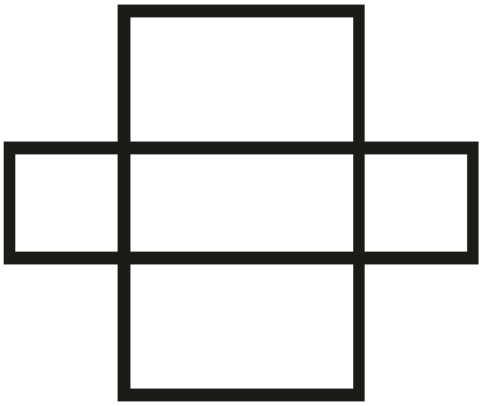

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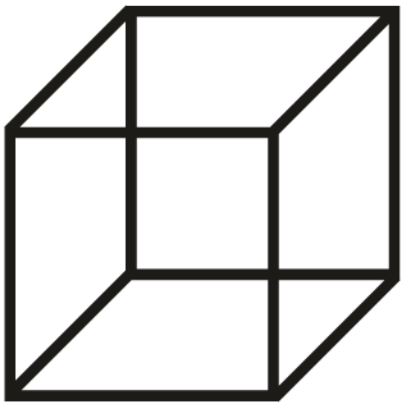

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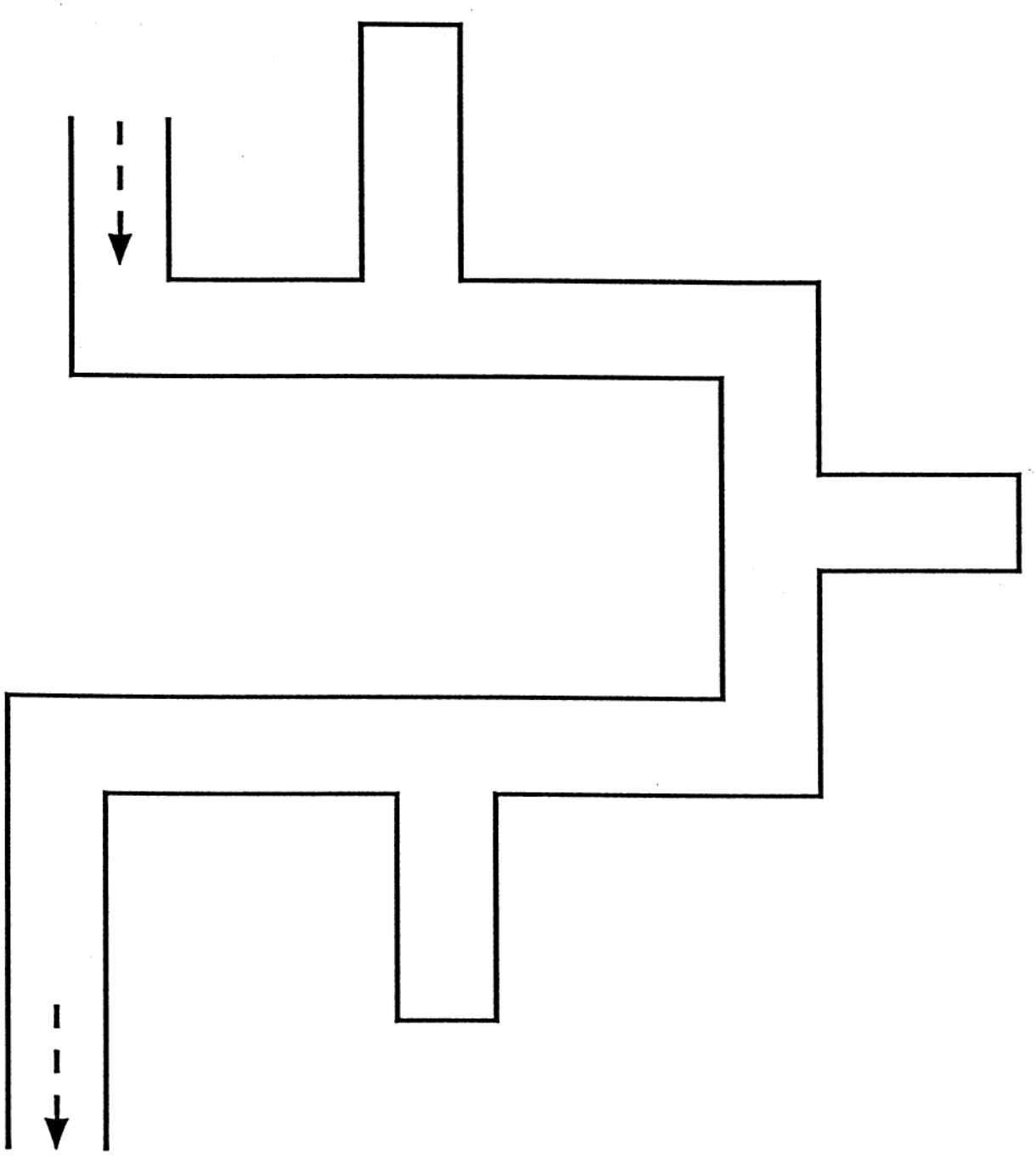
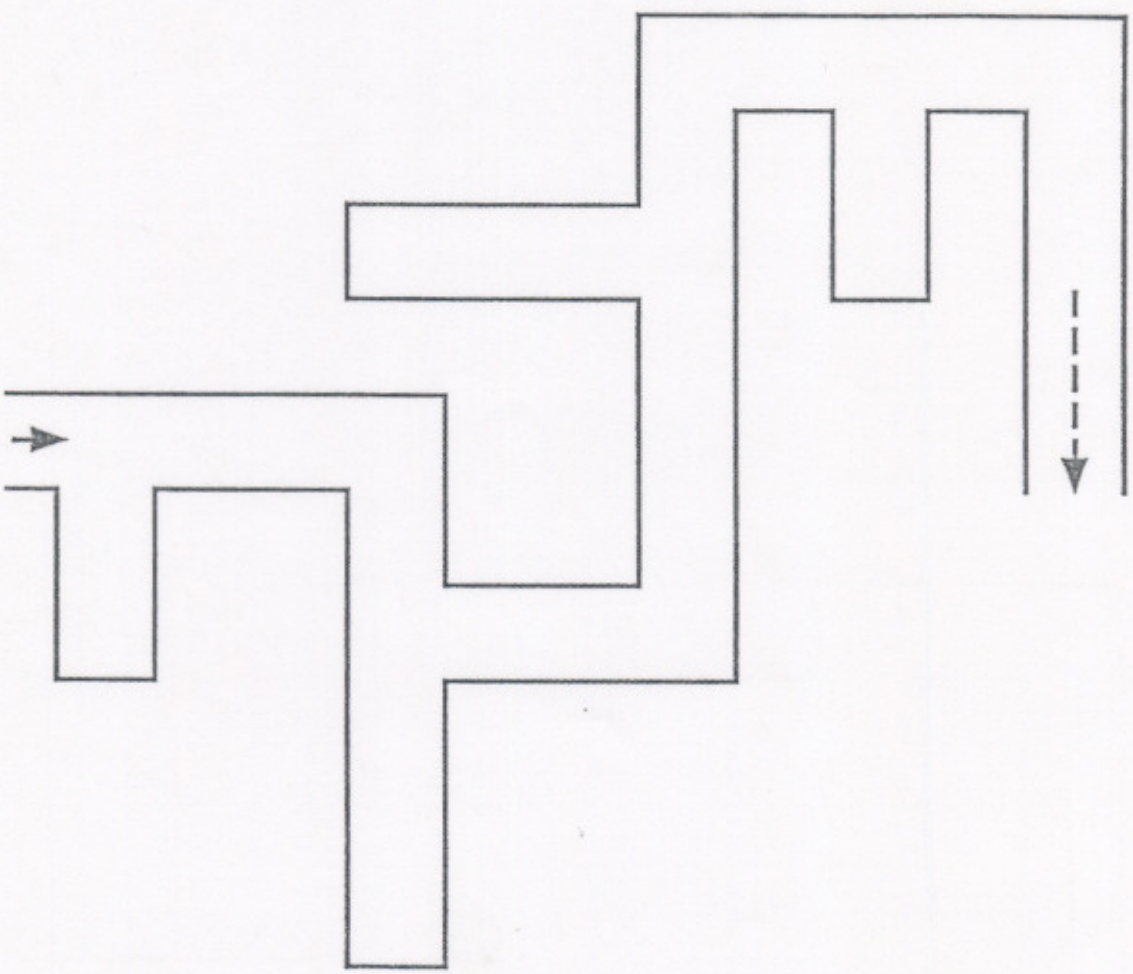


Example

A2



"6" and "1"

1 2 2 4 5 9 5 6 6 9 1 9 6 7 8 3 2 4 3 7 2 1 4 2 2 1 2 6 6 3

Example for use with versions A, B, and C

"2" and "8"

6 2 6 7 2 3 1 3 8 5 5 5 8 1 7 9 1 7 2 7 4 5 7 6 1 3 9 6 2 1

9 4 6 9 5 7 1 8 9 5 6 5 4 2 7 1 5 2 7 9 1 7 1 1 1 4 2 8 5 8

1 9 7 9 7 1 6 7 8 6 5 5 7 2 9 6 5 9 5 4 7 3 2 4 5 6 1 4 3 4

4 6 8 4 1 4 1 7 2 4 7 1 7 6 7 5 4 9 8 7 5 6 2 1 6 9 3 1 4 8

7 8 6 7 1 7 1 3 4 3 9 8 6 5 1 8 3 4 2 6 9 9 6 1 6 4 3 9 3 4

4 9 3 8 7 2 5 4 4 8 7 6 4 1 4 7 2 6 8 7 5 6 3 2 6 4 4 6 8 4

4 8 3 4 7 5 4 4 7 9 7 3 6 8 6 5 4 7 4 3 4 9 2 5 3 5 4 7 3 5

4 9 3 3 8 1 8 4 2 6 5 6 6 1 7 2 4 2 9 7 9 7 6 1 5 1 4 1 9 8

A

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ADAS

Administration Manual for the Alzheimer's Disease Assessment Scale

Adapted from the Administration and Scoring Manual for the
Alzheimer's Disease Assessment Scale,
1994 Revised Edition, Richard C. Mohs, Ph.D.

Present manual modified by:
Donald Connor, Ph.D
Kimberly Schafer, MS
(3/98)

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INTRODUCTION

The test items on the cognitive part of the **ADAS** should be given in the order indicated.

The WORD RECALL test is given first
and the
***WORD RECOGNITION* task is given last**
with the
other cognitive tests given in-between.

Separating the two word memory tasks in this way minimizes the chance that a subject will confuse the words from the two tasks.

At the start of a test session, before giving the **WORD RECALL** test, the tester should have a short conversation with the subject about neutral topics such as the weather, the subject's trip to the clinic, or what the subject had for breakfast. This conversation will help to put the subject at ease before the testing begins and will give the tester an opportunity to observe how the subject can use and understand language.

- There are three clinical ratings of language ability on the cognitive part of the **ADAS**.

The **ADAS** is not a timed test and the subject's score does not depend upon how rapidly the test is completed. The cognitive items should be given so that the session moves smoothly and quickly, but not so that the subject feels pressured to respond rapidly.

Feedback to the subject should be neutral and, usually, should not indicate whether or not the response was correct. Comments such as, **"That's fine"** or **"You're doing well"** are appropriate as long as the subject is trying. If the subject specifically asks whether or not they were correct, feedback can be given.

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ADAS

INSTRUCTIONS for WORD RECALL TASK

On this task, the subject is given three trials to learn a list of high-frequency, high-imagery nouns. The 10 words are printed in block letters on white cards.

Use the appropriate word list for each visit as indicated on the study worksheet, and record the subject's responses on the study worksheet.

At the start of the first trial, the tester gives instructions similar to the following:	**"I am going to show you some words printed on these white cards one at a time. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready, read the word and try to remember it."**
The examiner can prompt with:	**"Read it out loud and try to remember it"** as necessary.

If the subject cannot read the word or is slow, the examiner can say the word out loud and have the subject repeat it. Note this and continue with this procedure at each testing. In some cases, the examiner may have to say all of the words and have the subject repeat them. Regardless, make sure the subject looks at each word while repeating it.

After the presentation, the tester asks the subject to try to recall as many of the words as possible by saying:	**"Good, now tell me all the words you remember that were on the list."**

Two more learning and recall trials follow.

For trials 2 and 3, say to the subject:	**"Now I'm going to show you that same list again. Read each word out loud and try to remember it."**

Encouragement can be given if the subject is nervous or giving up.

SCORING:

The subject's score is the mean number of words *not* recalled on three trials (maximum score = 10)

Enter the subject's score on the study worksheet

ADAS

INSTRUCTIONS for NAMING TASK

For this task, the subject is asked to name the 12 randomly presented real objects, with
high (Flower, Bed, Whistle, Pencil),
medium (Rattle, Mask, Scissors, Comb), and
low (Wallet, Harmonica, Stethoscope, Tongs) **frequency values.**

The subject is also asked to name the fingers on his/her dominant hand.

- Use the study worksheet to record the subject's responses.
- Objects should be presented in random order. Do not allow the subject to touch the objects.

Give the subject instructions similar to the following:	**"Now I am going to show you some objects. I want you to tell me what their names are. What is this called?"** (present object)
Continue to present objects in random order. The first question about each object should be:	**"What is this called?"** or **"What is the name of this thing?"**
If the subject responds with the object's function say:	**"Yes, that's what it does, but what is its name?"**

- If the subject does not respond, the examiner should give the clue for that item provided below. If the subject still does not respond or makes an error, go on to the next object.

ITEM	CLUES
Flower	grows in a garden
Bed	used for sleeping in
Whistle	makes a sound when you blow on it
Pencil	used for writing
Rattle	a baby's toy
Mask	hides your face
Scissors	cuts paper
Comb	used on hair
Wallet	holds your money
Harmonica	a musical instrument
Stethoscope	doctor uses it to listen to your heart
Tongs	picks up food

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INSTRUCTIONS for NAMING TASK (Cont'd.)

➲ The subject is also asked to name the fingers of his/her dominant hand (*e.g.,* thumb, index [pointer/forefinger], middle, ring finger, and pinky).

Give the subject instructions similar to the following:	**"Now I am going to point to a part of your hand and I want you to tell me what it's called. What is this?"**
For the 4 fingers, if a query is necessary, say:	**"What is another name for this finger?"**

ITEM
Thumb
Index/forefinger/pointer
Middle
Ring
Pinky

The hardest part of scoring the naming task is determination of the range of correct responses based on the subject's cultural and geographical background. A response other than the name given on the response form should be scored as correct if it is a name that would be used by a non-demented person with the same cultural background as the subject.

FOR EXAMPLE: the **Mask** might be called a **"false face"** in some parts of the U.S.; the **Wallet** might be called a **"billfold"** or the **Harmonica** might be called a **"mouth organ"**.

➲ Descriptions of the object, semantic or phonemic paraphasias should not be scored as correct.

EXAMPLES OF INCORRECT RESPONSES ARE: **"listening thing"** for **Stethoscope,** **"cutter"** for **Scissors,** and **"prongs"** for **Tongs.**

SCORING	
0 = 0-2	items (objects and fingers) named incorrectly
1 = 3-5	items (objects and fingers) named incorrectly
2 = 6-8	items (objects and fingers) named incorrectly
3 = 9-11	items (objects and fingers) named incorrectly
4 = 12-14	items (objects and fingers) named incorrectly
5 = 15-17	items (objects and fingers) named incorrectly
Enter the subject's score on the study worksheet.	

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INSTRUCTIONS for COMMANDS

This task is designed to assess receptive speech. The subject is asked to carry out 5 separate commands with 1 to 5 steps per command.

- Each command should be read once. If the subject does not respond or makes an error, the tester should give the ***ENTIRE*** command one more time.
- All commands should be given to every subject.
- If the subject demonstrates hearing or attentional difficulties, orient them by saying, **"Ready?"** or **"Now I want you to..."** prior to giving the command. Do ***NOT*** give the command more than twice.
- There should be no other materials near the pencil, watch and card (pens, paper, etc.)
- Each underlined element represents a single step.
- Each command is scored as a whole (no partial credit). All components must be correct for the response to be scored as correct.
- Use the study worksheet to record the subject's responses.

Give the subject instructions similar to the following:	**"Now I am going to ask you to do a few things. First, ...** **"Make a *FIST*."** (**"Relax it"** if needed) **"Point to the *CEILING* and then to the *FLOOR*."**
Line up a Pencil, Watch, and Card on the table. Say:	**"Put the *PENCIL ON TOP OF THE CARD* and then *PUT IT BACK*."** **"Put the *WATCH* on the *OTHER SIDE OF THE PENCIL* and then *TURN OVER THE CARD*."**
Remove the Pencil, Watch, and Card from the table. Say:	***"TAP EACH SHOULDER TWICE* with *TWO FINGERS* keeping your *EYES SHUT*."**

SCORING	
0 =	All commands correct
1 =	1 command incorrect, 4 commands correct
2 =	2 commands incorrect, 3 commands correct
3 =	3 commands incorrect, 2 commnads correct
4 =	4 commands incorrect, 1 command correct
5 =	All 5 commands correct

Enter the subject's score on the study worksheet

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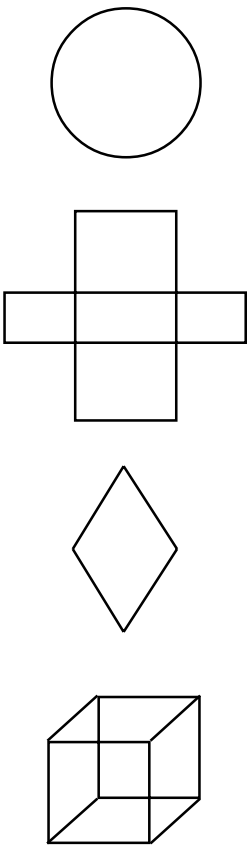
INSTRUCTIONS for CONSTRUCTIONAL PRAXIS

This test assesses the subject's ability to copy 4 geometric forms ranging from a very simple one (circle) to a fairly difficult one (cube).

- Use the study worksheet to score the subject's responses.
- The forms provided should be presented one at a time.
- The tester should give the subject a lead pencil with an eraser along with the drawing.

The instructions to the subject should be similar to the following:	**"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page."** (Examiner may point to shape)
If the subject's response is quick or sloppy, prompt with:	**"Take your time and try to draw it just like this one."**

- The subject should be allowed **two attempts** for each shape. Allow a second attempt only if the subject asks or indicates a problem with their drawing. The subject may erase if they need to. If the subject draws on top of the printed design, count this as one attempt and indicate that they should try on an empty part of the page. If the subjects says the reproduction is poor, query if the subject wants another try. When two attempts are made, ask the subject to indicate which one is the best, and then score that attempt.
- If the subject cannot reproduce the figure in two attempts, the tester should go on to the next item.
- A drawing should be scored as correct if the subject has reproduced all of the essential features of the original. Changes in size do not count as errors. Small gaps between lines do not indicate an error, as long as the shape has been reproduced.



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INSTRUCTIONS for CONSTRUCTIONAL PRAXIS (cont'd)

The forms should be presented in the following order:

Circle
Two Overlapping Rectangles
Diamond (Rhombus)
Cube

SCORING GUIDELINES:

Circle: A closed curved figure

Two Overlapping Rectangles: Forms must be four-sided, and overlap must be similar to presented form. Changes in size are not scored.

Diamond (Rhombus): Figure must be four-sided, oriented so that the points are at the top and bottom, and the sides are approximately equal length (e.g., longest side is not ≥ 1.5 times the length of the shortest side).

Cube: The form is 3-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.

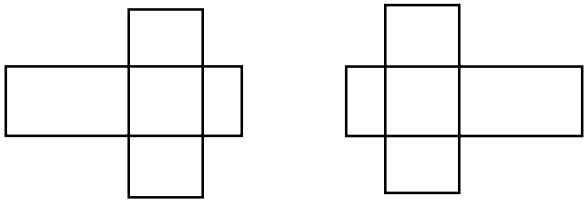
SCORING	
0 =	All 4 drawings correct
1 =	1 form drawn incorrectly
2 =	2 forms drawn incorrectly
3 =	3 forms drawn incorrectly
4 =	4 forms drawn incorrectly
5 =	No figures drawn, scribbles; parts of forms; words instead of forms

Enter the subject's score on the study worksheet

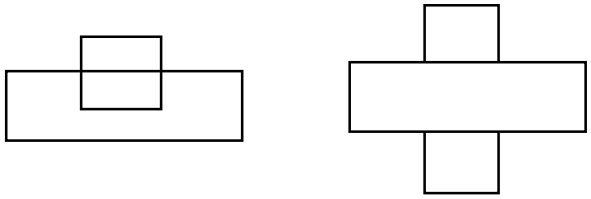
Examples of Correct and Incorrect Drawings:

Overlapping Rectangles

Correct

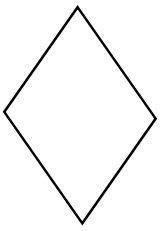


Incorrect



Diamond

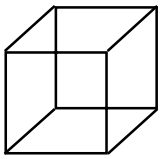
Correct



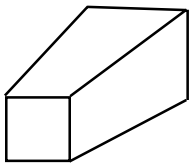
Incorrect

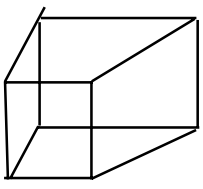
Cube

Correct



Incorrect





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INSTRUCTIONS for IDEATIONAL PRAXIS

This task is designed to determine whether the subject can perform a familiar but complex sequence sequence of actions.

- Use the study worksheet to record the subject's responses.
- A long envelope, an 8.5" x 11" sheet of paper and a pencil are placed in front of the subject.

Give the subject instructions similar to the following:

"I want you to pretend you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then, seal the envelope, address the envelope to yourself, and show me where the stamp goes."

- There are 5 components to this task and each one is underlined in the instruction.
- If the subject forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the subject is having difficulty.

FOR EXAMPLE: If the subject stops after folding the paper and putting it in the envelope, the tester should give **one reminder** on the next component:, **"Now seal the envelope."** If the subject cannot do this part, move on and give one reminder on the next component:**"Now address the envelope to yourself."**

After the first complete instruction only one additional reminder should be given for each component.

- Impairment on this item should reflect dysfunction in executing an overlearned task only and not recall difficulty.
- Any address which would enable a postal worker to deliver the envelope is counted as correct, even though it might not contain the subject's current address. The address should contain: name, street, city, and state. Zip code is not required.
- Have the subject indicate where the stamp goes by placing an "X" on the envelope.

SCORING	
0 =	All components performed correctly
1 =	Failure to perform 1 component
2 =	Failure to perform 2 components
3 =	Failure to perform 3 components
4 =	Failure to perform 4 components
5 =	Failure to perform 5 components

Enter the subject's score on the study worksheet

ADAS

INSTRUCTIONS for ORIENTATION

This task is designed to determine how well oriented the subject is with regard to time and place.

- Use the study worksheet to record the subject's responses.
- The components of orientation are:

Person
Day of the Week
Date, Month, Year
Season
Time of Day
Place

- The tester should ask the subject for each of these pieces of information one at a time.
- Make sure no watches, clocks, calendars, etc. are visible to the subject.
- One restatement of question is allowed (*e.g.*, if subject confuses day and date).
- Acceptable range for answers include:

Date:	+ one day
Time:	+ one hour
Place:	Partial name acceptable (*e.g.*, name of hospital, clinic or professional building)
Season:	Within one week prior to onset or within two weeks of termination

- **Month, Year, Day of the Week**, and the **subject's first and last name** must be **exact.**

SCORING: One point is given for each incorrect response (maximum = 8)

- Enter the subject's score on the study worksheet.

ADAS

INSTRUCTIONS for WORD RECOGNITION

On this task the subject is given one trial to learn a list of 12 words.

- Use the appropriate word list as indicated on the study worksheet, and record the subject's responses on the study worksheet.
- The learning part of this trial is similar to the learning part of the WORD RECALL TEST since the subject is asked to read each word aloud and try to remember it.
- For the one test trial, the 12 studied words are mixed with 12 new words matched to the studied words for frequency and imagery and the subject is asked to decide for each word whether or not it was one of the studied words.

At the start of the Learning Trial, give the subject instructions similar to the following:	**"I am going to show you some words printed on these white cards. I want you to read each word out loud and try to remember it."**

Some of the words on the WORD RECOGNITION TASK may not be familiar to the subject and the subject may have difficulty reading them. If the subject cannot read a word, the tester should say the word out loud. However, it is important for the subject to actually look at each word and try to read it.

At the end of the learning portion of a trial the tester should say something to the subject similar to the following:	**"Now I'm going to show you another set of words. Some of the words were on the list I just showed you and others are new. For each word I want you to tell me whether it is one of the words I just showed you."**
The tester shows the first word and says either: or:	**"Is this one of the words I showed you before, yes or no?** **"Did I show you this word before?"**
The same instruction is given before the second test word. For the remaining test words the tester should say:	**"How about this one?"**

ADAS

INSTRUCTIONS for WORD RECOGNITION (cont'd)

- If the subject does not remember the task (*e.g.*, reads the word rather than responding **"Yes"** or **"No"**) then the tester should repeat or rephrase the entire question and make a note in the appropriate column on the worksheet that the subject had to be reminded of the task instructions. Likewise, if the subject appears to have fallen into a response set (*i.e.*, saying **"Yes"** to every word or saying **"No"** to every word), then the test instructions should be repeated.

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INSTRUCTIONS for REMEMBERING TEST INSTRUCTIONS

This item evaluates the subject's ability to remember the requirements of the WORD RECOGNITION TASK.

On each recognition trial, the subject is asked prior to presentation of the first two words:	**"Did I show you this word before, or is this a new word?"**
For the third word, the subject is asked:	**"How about this one?"**

- If the subject responds accurately, *i.e.*, **"Yes"** or **"No"**, then memory for the instructions is accurate.
- If the subject fails to respond, this signifies that the instructions have been forgotten and the instruction is repeated.
- The procedure used for the third word is repeated for words 4-24. Each instance of memory failure for the test instructions is noted.

SCORING	
0 =	Subject never needs extra reminders of instructions
1 =	Very mild – forgets once
2 =	Mild – must be reminded 2 times
3 =	Moderate – must be reminded 3 or 4 times
4 =	Moderately severe – must be reminded 5 or 6 times
5 =	Severe – must be reminded 7 or more times
Enter the subject's score on the study worksheet	

ADAS

INSTRUCTIONS for SPOKEN LANGUAGE ABILITY

This item is a global rating of the quality of speech, *i.e.*, clarity, difficulty in making oneself understood.

- In rating this item the tester should consider all of the speech produced by the subject during the test session.
- Quantity of speech and word finding difficulty are not rated on this item.
- It should be noted that the higher scores (4-5) on this item are reserved for subjects whose expressive language abilities are impaired to such an extent that they seldom communicate without difficulty.

SCORING	
0 =	No instances when it is difficult to understand the subject
1 =	Very mild – one instance of lack of understandability
2 =	Mild – subject has difficulty less than 25% of the time
3 =	Moderate – subject has difficulty 25-50% of the time
4 =	Moderately severe – subject has difficulty 50% of the time
5 =	Severe – one or two word utterance; fluent, but empty speech; mute

Enter the subject's score on the study worksheet

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INSTRUCTIONS for WORD-FINDING DIFFICULTY AND COMPREHENSION

Word-Finding Difficulty in Spontaneous Speech

Along with Spoken Language Ability, this item rates impairment in expressive speech, but it rates ***only word finding difficulty***, whereas Spoken Language Ability is a more global rating of the extent to which the subject can communicate verbally.

- To rate this item, the tester must determine whether the subject has difficulty in finding the desired word in spontaneous speech. The problem may be overcome by circumlocution, *i.e.*, giving explanatory phrases or nearly satisfactory synonyms.
- Do not include finger and object naming in this rating.

SCORING	
0 =	No evidence of word finding difficulty in spontaneous speech
1 =	Very mild – 1 or 2 instances, not clinically significant
2 =	Mild – noticeable circumlocution or synonym substitution
3 =	Moderate – loss of words without comprehension on occasion
4 =	Moderately severe – frequent loss of words without comprehension
5 =	Severe – near total loss of content of words; speech sounds empty; 1 – 2 word utterances
Enter the subject's score on the study worksheet	

Comprehension — This item rates the subject's ability to understand speech

- To rate this item, the tester should consider how well the subject was able to understand the tester's speech during the opening discussion and during the test session
- Do not include responses to commands

SCORING	
0 =	No evidence of poor comprehension
1 =	Very mild – 1 or 2 instances of misunderstanding
2 =	Mild – 3-5 instances of misunderstanding
3 =	Moderate – requires several repetitions and rephrasing
4 =	Moderately severe – subject only occasionally responds correctly, *i.e.*, yes/no questions
5 =	Severe – subject rarely responds to questions appropriately, not due to poverty of speech
Enter the subject's score on the study worksheet	

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Development of Cognitive Instruments for Use in Clinical Trials of Antidementia Drugs: Additions to the Alzheimer's Disease Assessment Scale That Broaden Its Scope

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Summary: The cognitive assessment protocol of the Alzheimer's Disease Cooperative Study (ADCS) was designed to evaluate the reliability and validity of cognitive assessment measures that might be valuable additions to the Alzheimer's Disease Assessment Scale (ADAS) or other concise batteries used in antidementia drug trials. As part of an overall ADCS protocol to develop new instruments to be used in trials of treatments for Alzheimer's disease (AD), patients with mild to moderate AD and cognitively normal elderly were administered a battery of five tests at least three times over 1 year. The tests included word list learning with delayed free recall, a recognition memory test for faces, a series of letter and digit cancellation tests to measure concentration, tests of praxis, and a series of maze completion tasks designed to assess planning and executive function. A version of the digit cancellation task was reliable and sensitive to a broad range of dementia severity so that it could provide a useful addition to the present version of the ADAS. Performance on the word learning task with delayed recall and a subset of the mazes task were impaired even in mild AD, so these tasks may be useful in trials involving mild or at-risk subjects. Performances on the facial recognition task and on the praxis tasks were not related to dementia severity, so these tasks would not be useful to evaluate treatments. Therefore, the major outcome of this investigation was the identification of some potential addtions to the present ADAS that extend both the cognitive domains and the range of symptom severity covered. **Key Words:** Assessment scales—Alzheimer's disease—Cognitive impairment.

Although patients with Alzheimer's disease (AD) may have a variety of clinical symptoms, a progressive impairment in memory and other cognitive functions is their most prominent characteristic. Recent efforts to develop more effective treatments for AD have been concerned primarily with treatments that might improve cognitive function or, possibly, slow the rate of cognitive decline. As knowledge about the pathophysiology of AD has improved and as the number of potential new drug treatments has increased, the assessment of the cognitive effects of drug treatments has also evolved. Early clinical trials used measures borrowed from the diagnostic neu-

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ropsychology laboratory (Yesavage et al., 1979) whereas more recent studies have used one or two comprehensive instruments specifically designed to grade the severity of dementia such as the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Alzheimer's Disease Assessment Scale (ADAS) (Rosen et al., 1984). The advantages of a single instrument are several. They include efficiency of administration, restricted time demands for patients, conservation of statistical power, and simplicity of interpretation.

The ADAS was developed with these features in mind, specifically for longitudinal assessment of AD patients. It has been widely used and well received. However, the ADAS does not contain certain cognitive elements that, in retrospect, might be important. In particular, the ADAS does not include any tests designed to assess attention and concentration, nor does it include any specific assessment of planning or executive functions, both of which may be impaired. Although the ADAS does assess memory in some detail, recent work (Welsh et al. 1991; Petersen et al., 1995) indicates that aspects of verbal memory such as delayed recall, which were not included in the ADAS, are important for measuring memory impairment early in the course of dementia. Memory for nonverbal material probably has a different biologic substrate than does verbal memory, and the ADAS does not include any tests of nonverbal memory. Finally, praxis can be assessed in a variety of different ways (Goodglass and Kaplan, 1972), most of which are not included in the ADAS.

The purpose of the present investigation was to investigate the validity and reliability of cognitive measures that assess those aspects of cognitive function not represented in the ADAS. The overall design of the ADCS instrument protocol enabled us to obtain the following information about each of these proposed new tests:

1. What is the 1-month test–retest reliability of the test?
2. To what extent is test performance affected by learning, as might occur in a treatment trial when patients are tested repeatedly?
3. Are there confounding effects of age and education on change scores?
4. How useful is the test across the spectrum of disease severity?
5. How sensitive is the test to change over 12 months, and how variable is that change?

METHODS

Overview

A detailed description of the design of the ADCS Instrument Study Protocol and of the study participants is given in the article by Ferris et al. (this issue). Subjects who participated in the cognitive instrument protocol included 64 normal elderly control (NEC) subjects, 50 mild AD patients with baseline MMSE scores ≥21 (group AD I), 47 moderate AD patients with baseline MMSE scores of 16–20 (group AD II), and 46 moderately severe AD patients with baseline MMSE scores of 10–15 (group AD III). Half of the patients in each severity group were tested at baseline, and at 1, 2, 6, and 12 months, and the other half were tested at baseline, 1, 6, and 12 months. Whenever possible, different forms of the tests were given at each test session.

The standard instruments used to characterize the severity of dementia in all subjects are described in the article by Ferris et al. (this issue). They include the Clinical Dementia Rating (CDR; Hughes et al., 1982), the Global Deterioration Scale (GDS; Reisberg et al., 1982), and the MMSE (Folstein et al., 1975).

New Instruments

The novel cognitive instruments tested in this study were administered in the order in which they are described below. Before the study was initiated, a detailed Administration and Scoring Manual was developed to help psychometricians at the ADCS sites administer and score the tests in a uniform manner. In addition, a videotape showing a standard administration of the test battery was made and distributed to all sites. Questions concerning administration and scoring that arose during the conduct of the study were answered promptly by the ADCS Cognitive Instrument Committee and updates to the Manual were distributed to all sites.

Word List Learning

For this task, the subject was given four trials to learn a list of 10 concrete nouns. The methods were similar to those used both by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989) and the ADAS (Rosen et al., 1984). Each of the 10 words was printed in large letters on a card. Subjects were shown the cards one at a time for 2 s each, and the subject was instructed to read each word aloud. If the subject could not read or misread a word, the examiner read it aloud. After the list was read, the subject was asked to recall the words aloud. Five different word lists, equated for mean frequency of occurrence (Thorndyke and Lorge, 1944) and for imagery (Pavio et al., 1968), were used for the five test sessions.

Praxis

The items used for tests of praxis were drawn from the Boston Diagnostic Aphasia Examination (Goodglass and

Kaplan, 1972). The subjects were told that they would be asked to follow some instructions. They were then asked to perform two facial commands (e.g., sniff a flower), two upper limb commands (e.g., wave goodbye), two instrumental commands (e.g., stir coffee with a spoon), and two whole-body commands (e.g., march like a soldier). Performance was scored from 0 to 3 according to the following criteria: 3 points, good performance on command; 2, approximate performance on command or good performance on imitation; 1, approximate performance on imitation or uses body part as object (e.g., uses hand as the instrument); and 0, cannot perform task. Four different forms of this task were used and subjects received the same form at baseline and 12 months. The subject's total score ranged from 0 to 24.

Delayed Verbal Recall

For this task, the subject was asked to recall as many words as possible from the previously studied list. This task is similar to the delayed recall procedure used in the CERAD battery (Welsh et al., 1991). The subject's score was from 0 to 10.

Facial Recognition Memory

This task used stimuli and procedures adapted from Warrington and James (1967). During the learning phase, 12 black-and-white pictures showing only a person's face were presented at a rate of one picture every 3 s. To ensure that the subjects attended to the picture they were asked to judge whether the faces were pleasant or not. Immediately after the 12 faces had been presented, 12 pairs of faces were then presented, and for each, the subject was asked to point to the face that had been shown previously. Four alternative forms were constructed from the total pool of stimuli developed by Warrington and James (1967), so that form 1 was used at baseline and then again at month 12 for all subjects. The subject's score was the number of correct responses out of 12.

Cancellation Test

This task was adapted from paradigms used in cognitive (Neisser, 1964) and clinical neuropsychology (Lezak, 1982) that are designed to assess visual attention and concentration. In this task, the subject was presented with a page on which there were eight rows on letters or digits and the subject's task was to cross off as many target letters or digits as possible in 60 s. Because the difficulty of this task depends on the target, subjects were given six different versions in each session and for each the target was printed at the top of the page. A practice task was given to the subjects before beginning the task. Subjects were told to work as quickly as possible and were told not to erase if they crossed off an incorrect letter or number. The tester was allowed to remind subjects of the instructions if they made three errors in a row or forgot the instructions during the task. The six versions of the task were: (a) single letter (e.g., "P") mixed with other letters; (b) pair of two letters (e.g., "O E") mixed with other letters; (c) either of two letters (e.g., "L" or "T") mixed with other letters; (d) set of three letters (e.g., "W K M") mixed with other letters; (e) large letters (e.g., "E") mixed in with letters printed in normal size type; and (f) either of two numbers (e.g., "2" or "8") mixed in with other numbers.

There were 13–40 targets on each page depending on the test version (see Table 3). The subject's score was the number of target items correctly crossed off in 60 s minus the number of incorrectly crossed off items, and minus the number of reminders given. Four alternate forms of each task were available, so that form 1 was used at baseline and then again at month 12.

Maze Test

Paper and pencil mazes and instructions were drawn from the battery of Christensen et al. (1991). Seven mazes of increasing complexity were presented in each session. Complexity was increased by increasing the number of turns that had to be made to draw a line from start to finish without crossing a maze boundary. Subjects were instructed to find their way through each maze with a pencil, without hitting a dead end, and were told that they could pause to make a decision. They were told to proceed as quickly as possible because the task was being timed. An example was given for practice at the beginning of the task and again just before the fourth maze. In the examples, the subjects were shown the entrance and exits to the practice mazes and were told not to lift their pencil from the paper. After hitting a dead end for the first time, the examiners would bring the subject back to the point of the incorrect decision and suggest that the subject try another direction. After hitting a second dead end, the examiner would go on to the next maze. After two consecutive mazes with two dead ends, the task was halted. If the subject did not complete a maze in 240 s the examiner went on to the next maze. The number of mazes completed and the times to completion were recorded. Four alternate forms of this test were available, so that form 1 was used at baseline and then again at month 12.

RESULTS

Overview

For each of the measures, we performed analyses designed to address each of the issues raised in the introduction. To assess reliability, both Pearson and Spearman correlation coefficients were calculated but, because the two measures were very close in every case, only results from the Pearson calculations are reported. Similarly, the effect of confounds due to age and education were also estimated by Pearson correlations. The effect of learning on each measure was examined by looking at change over 1 month, a time period during which little meaningful clinical change would usually occur. A more detailed analysis of the effects of repeated exposure comparing the two testing schedules is beyond the scope of this first report. The ability of each test and measure to assess the full range of dementia severity was examined by looking at the extent to which scores differed across all severity groups and the extent to which there were ceiling or floor effects. Ability to measure longitudinal change was assessed by looking at 12-month change. For some measures a difference effect size measure (d), defined as the mean change divided by the standard deviation of the change, was used to provide an index of the relative sensitivity of that measure to longitudinal change. The value of this measure is that it takes mean change scores, which are originally expressed in different units (e.g., seconds, errors, number of words recalled), and expresses each in terms of standard deviation units, thus enabling us to compare across measures. As for any longitudinal study, data are sometimes not available for follow-up visits owing to missed visits, untestability, or errors in data recording. In each of the data tables discussed below we have listed, along with mean performance data, the number of patients in each group for whom valid data were available at baseline and at 12 months. The overall rate of missing data was low but increased with severity of dementia and duration of follow-up.

Word List Learning

Results for this task are presented in Table 1. The 1-month retest reliability was $r = 0.79$, 0.86, 0.84, and 0.86 for trials 1–4, respectively. For the sum of trials 1–4 the Pearson r was 0.92. There clearly was no learning effect at 1 month, because most scores were slightly lower than at baseline. There were no significant correlations between age or education and any of the 12-month change score values for the four learning trials.

Baseline performance was different for all four severity groups indicating that, at least for the sum score, this task discriminates a broad range of dementia severity. Even among the NEC group there was relatively little evidence of a ceiling effect, except for trials 3 and 4. For patients in the most severe group (AD III), performance after 12 months was very poor, with 37% of patients giving no response and an additional 30% recalling a total of four or fewer words. Normal controls usually improved their performance slightly at the 1-year follow-up, whereas patients in all three AD groups showed worse performance on all trials. Because some word list learning paradigms use three trials (Morris et al., 1989) and others use more (Petersen et al., 1995), we compared the effect sizes (d) for the sum of three and four trials for AD I patients, in whom there were no ceiling or floor effects. For AD I patients the d for the sum of trials 1 to 3 was 0.72 and d for the sum of trials 1 to 4 was 0.73, suggesting that inclusion of the fourth trial did not add to the ability of the task to detect change.

Delayed Recall

Retest reliability was excellent for the delayed recall score ($r = 0.93$), but the (trial 5 − trial 4) difference score was less reliable ($r = 0.61$). As indicated by the data in Table 1, there appeared to be no learning effect, because scores after 1 month were slightly lower than baseline for all groups. There was no significant correlation of age or education with the 12-month change score.

As has been found in previous studies (Welsh et al., 1991) the delayed recall measure was very good for discriminating the NEC group from AD I patients. However, because of floor effects this measure did not discriminate among the AD groups. Even among AD I patients, 20% recalled zero words at baseline and 45.5% recalled none at 12 months. Over half of the patients in AD groups II and III recalled zero words at baseline and, at 12 months, 71% of AD II patients and 83% of AD III patients recalled zero words. As Table 1 indicates, there was relatively little change over 12 months in any of the AD groups because of low baseline performance.

Face Recognition Memory

The data for this task are presented in Table 2. The 1-month retest reliability for this task was poor ($r = 0.48$) but, as Table 2 indicates, there was no learning or other change in average performance over 1 month. Age was not associated with the 12-month change score ($r = -0.06$; $p = 0.43$), and there was no association of change with education ($r = 0.08$; $p = 0.29$). As Table 2 indicates, AD groups II and III performed very close to

TABLE 1. *Results of the word list learning and recall task*

Group	Baseline: 1-month follow-up subjects	1-month change score	Baseline: all subjects (*n*)	12-month score for all subjects (*n*)	12-month change (SD)
Trial 1 (0–10)					
NEC	6.21	−0.59	6.22 (64)	6.35 (62)	0.10 (1.77)
AD I	2.92	−0.24	3.20 (50)	2.27 (44)	−0.93 (1.81)
AD II	2.26	−0.38	2.36 (47)	1.48 (40)	−0.88 (1.13)
AD III	1.27	−0.11	1.29 (45)	.62 (29)	−0.66 (1.15)
Trial 2 (0–10)					
NEC	7.59	−0.13	7.70 (64)	8.23 (62)	0.50 (1.72)
AD I	4.40	−0.48	4.42 (50)	3.43 (44)	−0.98 (2.01)
AD II	3.66	−0.58	3.49 (47)	2.30 (40)	−1.19 (1.26)
AD III	2.32	−0.58	2.40 (45)	1.33 (29)	−1.07 (1.18)
Trial 3 (0–10)					
NEC	8.09	−0.53	8.17 (64)	8.52 (62)	0.32 (1.11)
AD I	5.24	−0.88	5.12 (50)	4.02 (44)	−1.02 (1.53)
AD II	4.25	−1.08	4.11 (47)	2.75 (40)	−1.36 (1.76)
AD III	2.42	−0.05	2.64 (45)	1.55 (29)	−1.04 (1.17)
Trial 4 (0–10)					
NEC	8.40	−0.09	8.67 (64)	8.65 (62)	−0.05 (1.22)
AD I	5.20	−0.24	5.32 (50)	3.89 (44)	−1.43 (2.26)
AD II	3.95	−0.58	4.11 (47)	2.65 (40)	−1.46 (1.55)
AD III	2.78	0.11	2.69 (45)	1.52 (29)	−1.09 (1.39)
Sum of trials 1–4 (0–40)					
NEC	30.25	−1.34	30.77 (64)	31.74 (62)	0.97 (3.98)
AD I	17.76	−1.84	18.06 (50)	13.61 (44)	−4.45 (5.92)
AD II	14.12	−2.63	14.06 (47)	9.18 (40)	−4.89 (4.27)
AD III	5.79	−.63	9.02 (45)	5.00 (29)	−4.02 (3.80)
Delayed recall (0–10)					
NEC	7.75	−0.22	8.02 (64)	8.48 (61)	0.41 (1.16)
AD I	2.40	−0.16	2.30 (50)	1.45 (44)	−0.89 (1.74)
AD II	1.54	−0.63	1.36 (47)	0.60 (42)	−0.76 (1.38)
AD III	0.84	−0.37	0.71 (45)	0.20 (30)	−0.48 (0.99)

NEC, normal elderly control; AD-I, MMSE ≥ 21; AD-II, MMSE 16–20; AD-III, MMSE 10–15.

chance levels at baseline, whereas AD group I's performance was better. However, substantial numbers of subjects in all three groups performed at chance levels at baseline (12%, 23%, and 35%, respectively). By month 12 the proportion of individuals scoring at chance increased in each group. Of the NEC, 52% scored perfectly at baseline. By month 12, 36.9% of AD patients remaining in the study scored at chance levels, whereas 48% of NEC scored perfectly. For NEC subjects and AD I patients, there was virtually no change over 1 year. The change for AD group II was small, and only in the AD III group was the mean change even close to the size of the standard deviation ($d = 0.89$).

Cancellation Test of Visual Attention and Concentration

Results for each of the kinds of cancellation task are presented in Table 3. One-month retest reliabilities were excellent ($r > 0.86$) for the Single Letter, Pair of Letters, and Either of Two Numbers tasks, good ($r = 0.90$) for the Either of Two Single Letters task, and slightly less

TABLE 2. *Results of the face recognition memory task*

Group	Baseline: 1-month follow-up subjects	1-month change score	Baseline: all subjects (*n*)	12-month score for all subjects (*n*)	12-month change (SD)
Number correct (0–12)					
NEC	11.03	−0.44	11.13 (64)	11.08 (62)	−0.05 (1.21)
AD I	8.68	0.08	8.90 (50)	8.53 (45)	−0.16 (2.54)
AD II	7.04	0.29	7.68 (47)	6.90 (41)	−0.88 (2.48)
AD III	7.33	−0.83	7.37 (43)	6.16 (25)	−1.92 (2.16)

Abbreviations as in Table 1.

TABLE 3. *Results of the letter cancellation task*

Group	Baseline: 1-month follow-up subjects	1-month change score	Baseline: all subjects (*n*)	12-month score for all subjects (*n*)	12-month change (SD)
Single Letter "P" (0–40)					
NEC	30.34	7.19	30.31 (64)	31.82 (62)	1.27 (3.52)
AD I	22.01	7.75	23.16 (49)	19.76 (45)	−3.39 (5.34)
AD II	16.00	5.46	16.30 (47)	11.95 (37)	−4.49 (6.31)
AD III	8.81	6.61	10.45 (44)	6.67 (24)	−3.21 (4.78)
Either of Two Single Letters "L" or "T" (0–40)					
NEC	23.97	4.81	23.83 (64)	25.69 (62)	1.63 (4.57)
AD I	13.68	4.16	14.42 (50)	12.40 (45)	−2.22 (4.09)
AD II	10.04	1.79	10.11 (47)	7.49 (37)	−2.62 (4.86)
AD III	4.32	2.00	5.89 (44)	3.38 (24)	−2.62 (4.04)
Pair of Letters "OE" (0–20)					
NEC	18.09	−0.47	18.19 (64)	18.08 (62)	−0.26 (2.34)
AD I	11.72	−1.40	11.78 (50)	9.60 (45)	−1.93 (3.93)
AD II	8.34	0.08	9.04 (46)	6.03 (37)	−2.72 (4.05)
AD III	3.64	1.22	4.67 (42)	3.50 (22)	−0.91 (1.95)
Set of Three Letters "WKM" (0–13)					
NEC	11.24	−2.13	11.36 (64)	11.37 (60)	0.06 (1.37)
AD I	8.20	−2.92	7.94 (50)	6.11 (45)	−1.76 (4.25)
AD II	5.25	−0.88	4.98 (47)	3.95 (37)	−1.08 (2.16)
AD III	2.65	−0.12	3.12 (41)	2.09 (22)	−0.95 (1.43)
Large Letter "LARGE LeTters" (0–40)					
NEC	33.25	3.47	34.17 (64)	38.73 (60)	4.77 (11.05)
AD I	24.84	−0.76	24.76 (50)	24.80 (45)	1.16 (11.76)
AD II	17.75	−3.04	19.57 (47)	13.78 (37)	−6.81 (9.36)
AD III	8.78	1.06	11.34 (41)	8.05 (21)	−3.38 (13.14)
Either of Two Numbers "2" or "8" (0–40)					
NEC	27.31	−0.59	27.22 (64)	28.61 (62)	1.26 (4.84)
AD I	18.48	−2.44	18.56 (50)	15.87 (45)	−2.60 (4.72)
AD II	12.79	0.46	13.62 (47)	10.35 (37)	−3.41 (4.90)
AD III	7.20	0.06	8.95 (40)	5.64 (22)	−3.23 (4.10)

Abbreviations as in Table 1.

good for the Set of Three Letters ($r = 0.72$) and Large Letters ($r = 0.74$) tasks. There were no significant correlations with age or education of 12-month change on any of these tasks. There appeared to be sizable learning effects over 1 month for the Single Letter and the Either of Two Single Letters tasks, in that month 1 performance was substantially better than baseline for both tasks. It is possible that these differences resulted from the specific targets used at baseline and 1 month. Further analyses of the two test sequences will be necessary to determine whether these changes are due to repeated exposure to the test or to the specific targets used.

Table 3 indicates that all versions of this task differentiated among the four groups, although the overall difficulty level varied by task. Mean performance of the NEC group was highest for the Pair of Letters task and lowest for the version with either of two single letters as targets. The 12-month change scores indicate that performance was either unchanged or improved somewhat in NEC subjects, whereas performance declined in most AD groups on all versions. On balance, it appears that the change scores were most robust in the cancellation task for Either of Two Numbers, and there is little that the other versions of this task added to the data obtained with the Either of Two Numbers version.

Maze Completion Test of Executive Function

Table 4 presents data on the number of mazes completed by subjects in each group at baseline and at 12 months. Using the total number of mazes completed by each person as a score, the calculated 1-month retest reliability was very high ($r = 0.95$). There were no confounding effects of age or education on 12-month change scores for this measure. As indicated by the data at the bottom of Table 4, there was no substantial change in the mean number of mazes completed at the 1-month retest reliability session for any subject group (one-sample t test $p > 0.35$ in all cases).

As indicated by the data in Table 4, the more difficult mazes, starting with 4 and higher, were difficult enough that even some of the mildly demented AD patients could not complete them, particularly at 1 year. Hence, time measures would be of little use except for mazes

TABLE 4. *Results for the maze completion test of executive function*

	NEC	AD I	AD II	AD III
Percent completed at baseline				
Maze 1	100	100	100	89
Maze 2	100	100	100	87
Maze 3	100	100	96	76
Maze 4	100	96	81	54
Maze 5	100	92	60	35
Maze 6	98	62	32	26
Maze 7	94	38	28	17
Percent completed at month 12 visit				
Maze 1	97	90	81	54
Maze 2	97	90	81	43
Maze 3	97	88	74	33
Maze 4	97	82	55	22
Maze 5	97	66	38	13
Maze 6	97	46	21	11
Maze 7	92	36	17	07

Group	Baseline: 1-month follow-up subjects	1-month change score	Baseline: all subjects (*n*)	12-month score for all subjects (*n*)	12-month change (SD)
Number of mazes completed					
NEC	6.87	−0.12	6.92 (64)	6.73 (64)	−0.19 (1.10)
AD I	5.76	−0.20	5.88 (50)	4.98 (50)	−0.90 (2.19)
AD II	4.63	0.08	4.96 (47)	3.68 (47)	−1.28 (2.22)
AD III	3.32	−0.23	3.85 (46)	1.83 (46)	−2.02 (2.33)

Abbreviations as in Table 1.

1–3, and then only in normals and patients with relatively mild AD. The overall number of mazes completed decreased over 12 months in AD patients but, given the amount of time required to present all mazes, it would not be practical to use this measure in any brief cognitive assessment.

Because so few patients, except for those in the AD-I group, were able to complete any mazes, most of the time to completion data are not useful. Table 5 presents time to completion data for the first (easiest) three mazes for the NEC and the AD-I patients who were able to complete them both at baseline and at 12 months. As the table indicates, NEC subjects were able to complete all three mazes more quickly than the AD-I patients and improved their performance slightly over 12 months. The AD-I patients, by contrast, were slower on all three mazes after 12 months.

TABLE 5. *Time scores for maze completion test*

Group	Baseline	12-month	12-month change (SD)
Maze 1 (seconds)			
NEC (n = 62)	2.9	2.4	−0.5 (3.9)
AD I (n = 45)	5.3	20.7	15.4 (49.3)
Maze 2			
NEC (n = 62)	5.5	5.2	−0.3 (2.7)
AD I (n = 45)	13.0	33.4	20.4 (59.7)
Maze 3			
NEC (n = 62)	27.2	26.6	−0.7 (11.5)
AD I (n = 44)	53.2	69.4	16.2 (59.4)

Abbreviations as in Table 1.

Praxis

Table 6 presents the mean scores on this test out of a maximal possible score of 24. Excluding NEC subjects, the retest reliability was modest (r = 0.48). However, there was one subject (an AD group III patient) who dramatically declined between baseline and month 1. Because it is likely his disease had progressed within that month and therefore violated the assumption of stability between test sessions, this individual was excluded from the analysis, resulting in a much more favorable retest reliability estimate of r = 0.72. Scores changed little from baseline to 1 month, indicating that practice effects were relatively small for this task, although performance in all but the most severe patients was near ceiling, which would limit the amount of improvement that could be detected. There were no confounding effects of age or education.

In contrast to the measures previously discussed, even AD group II and group III patients performed praxis commands so well at baseline that 48% and 22% of subjects, respectively, scored perfectly. However, by month 12, only 16% and 0% of AD group II and III patients were still performing at ceiling levels. Praxis was easy enough that floor performance occurred for

TABLE 6. *Number of correct responses on the praxis tasks*

Group	Baseline: 1-month follow-up subjects	1-month change score	Baseline: all subjects	12-month score for all subjects	12-month change (SD)
NEC	23.5	0.03	23.9	23.8	−0.10 (0.46)
AD I	23.9	0.68	23.2	22.4	−0.70 (2.47)
AD II	22.3	0.74	22.7	20.8	−1.90 (3.15)
AD III	20.1	0.89	20.5	16.7	−3.90 (4.78)

Abbreviations as in Table 1.

only one of the 13 AD group III patients still testable at month 12. The NEC group subjects overwhelmingly (more than 90%) performed at ceiling levels at baseline and at 12 months. Performance declined little over the 12 months of follow-up except for the most severe group of AD patients.

DISCUSSION

The goal of this study was to determine whether any of the present cognitive assessment procedures are likely to be of use in antidementia clinical trials. Ideally, a new measure would be reliable, sensitive to change, different from other standard measures, such those included in the ADAS, and free of floor and ceiling effects. Only one of the cancellation tasks clearly fitted that description entirely. Although not ideal in one respect or another, some of the other measures, such as the delayed recall and the simpler mazes measures, may be of use in selected circumstances.

Of the cancellation tasks the Either of Two Numbers task (task 6) may have been the most favorable, in that it showed no learning, was reliable, and showed declining performance over time in all three patient groups. It did not show ceiling effects at baseline either in the NEC group or the mildest AD group. Although AD group III scored much worse on this task than the milder patients, they were still largely above floor-level performance. Some of the other versions of the cancellation task might also be of use but would probably add little to what could be learned with the two-number task. A desirable feature of a cancellation task is that it requires little extra time to perform. Cancellation presumably requires attention and sustained concentration; it also requires subjects to maintain a cognitive "set" over time in the face of distraction. These cognitive functions are not explicitly represented on the ADAS.

The mazes were also potentially valuable, but the time necessary to administer all forms of the task make it difficult to incorporate into an instrument for treatment trials. The number of mazes completed was highly reliable, and there were no major confounds. There were ceiling effects in the NEC group but not in the AD patients. Maze performance is believed to be one of the prototypical executive functions, involving foresight, planning, maintenance of set, freedom from distraction, and reasoning. Again, those cognitive functions are not explicitly assessed on the ADAS. Because of the low rate of completion of the mazes in all but the mildest AD group the time measures were of little value. Only the times for the three simplest mazes might be of use, and then only in mild AD patients or, possibly, in those "at risk" for AD because of mild cognitive impairment.

The present experimental battery included a 4 trial list learning procedure coupled with delayed recall. Morris et al. (1989) and Welsh et al. (1994) have previously reported data for 10-word three-trial learning on CDR = 1 patients with 1-year follow-up. Our data offer a more refined view of the mildest patients (MMSE scores $\geq$21), who performed better than CDR = 1 patients. The present results demonstrate the reliability and responsiveness of list learning, especially in more mildly affected patients. Furthermore, the present results show that assessment of delayed recall over 1 year is feasible in mild AD patients. The fourth learning trial in verbal learning did not add much directly in terms of reliability or effect size to the present form of the ADAS, which uses three trials, but may have reduced the number of instances of floor performance. Delayed recall is the most sensitive measure for detecting early AD (Welsh et al., 1991). Longitudinal assessment of learning and memory with the enhanced procedures used here may be most important in mild AD patients and in patients with cognitive impairment without dementia (Morris et al., 1991; Locasio et al., 1995; Petersen et al., 1995), rather than in clinical trials that involve more severely affected patients. The addition of delayed recall and, possibly, the addition of a subset of mazes would help to make the ADAS more sensitive in mild cases, for which the current version is not particularly sensitive to change (Stern et al., 1994).

Praxis was unique among the functions we assessed in its suitability for measurement of the more demented patients. It was of little value in milder patients because of the likelihood of achieving perfect scores initially and not declining over 1 year. Although praxis might play a role in studies restricted to more advanced patients (patients with MMSE scores ≤15), it is not suitable for inclusion in an assessment battery intended for milder patients.

Facial recognition was a disappointment, in that a sizable proportion of AD groups II and III performed near chance levels at baseline. Furthermore, in AD group I there was virtually no change over 1 year. Because trials of some antidementia drugs are designed to detect effects on symptom progression rather than symptomatic improvement, the lack of sensitivity of this procedure suggests that it should not be used in clinical trials.

RECOMMENDATIONS FOR FUTURE COGNITIVE ASSESSMENT

On the basis of these results, the simplest addition to an instrument such as the ADAS would be the Either of Two Numbers cancellation task. It would add only a few minutes to ADAS administration and it could be scored by scaling the number of responses between 1 and 5. Based on the data from the four groups included in this study, the most useful scoring rule would be: ≥30 correct = 0; 24–30 correct = 1; 18–23 correct = 2; 12–17 correct = 3; 6–11 correct = 4; 0–5 correct = 5).

Inclusion of a cancellation task should not change the psychometric properties of the rest of the ADAS, although it will alter calculations of effect size based on prior work with the ADAS. A recent study that analyzed the predictive effects of different cognitive measures on instrumental ADL function emphasized visuoperceptual performance (in that case Poppelreuter's figures of overlapping objects) as being most useful (Hill et al., 1995). Adding cancellation, which has a visual perceptual component, may further strengthen the ADAS in this cognitive domain.

For clinical trials involving AD patients with MMSE scores >20 or involving cognitively impaired, nondemented individuals, four-trial learning plus delayed recall could be added to the ADAS-cog. For trials of "at risk" or very mild AD patients, one or two of the simplest mazes might be a useful addition.

For clinical trials involving AD patients with MMSE scores ≤15, praxis could be added to the battery. Further praxis items are probably not needed, however, because the Severe Impairment Battery (see Schmitt et al., this issue) includes praxis items.

The present attempts to bring measures of nonverbal memory (face recognition) into clinical trials assessments were not successful. Further work must be done to find procedures that are reliable and responsive.

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APPENDIX VII

AMYVID INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Amyvid safely and effectively. See full prescribing information for Amyvid.

Amyvid (Florbetapir F 18 Injection) for intravenous use

Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations (1).

Limitations of Use

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies (1).

DOSAGE AND ADMINISTRATION

Use appropriate radiation safety handling measures (2.1).

- Administer 370 MBq (10 mCi) as a single intravenous bolus in a total volume of 10 mL or less (2.2).
- Obtain 10-minute PET images starting approximately 30 to 50 minutes after intravenous injection (2.3).
- Image interpretation: Refer to full prescribing information (2.4).
- The radiation absorbed dose from a 370 MBq (10 mCi) dose of Amyvid is 7 mSv in an adult (2.5).

DOSAGE FORMS AND STRENGTHS

10 mL, 30 mL, or 50 mL multidose vial containing a clear, colorless injectable solution at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis (EOS) (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Image interpretation errors (especially false negatives) have been observed (5.1).
- Radiation risk: Amyvid, similar to all radiopharmaceuticals, contributes to a patient's long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure (2.1, 5.2).

ADVERSE REACTIONS

Most commonly reported adverse reactions were: headache (2%), musculoskeletal pain (1%), fatigue (1%), and nausea (1%) (6).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.

Limitations of Use:

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;

- Monitoring responses to therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

Amyvid is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration *[see Warnings and Precautions (5.1)]*. Use waterproof gloves and effective shielding, including lead-glass syringe shields when handling Amyvid. Radiopharmaceuticals, including Amyvid, should only be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radioactive materials, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

2.2 Recommended Dosing and Administration Instructions

The recommended dose for Amyvid is 370 MBq (10 mCi), maximum 50 µg mass dose, administered as a single intravenous bolus in a total volume of 10 mL or less. Follow the injection with an intravenous flush of 0.9% sterile sodium chloride.

- Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter or is discolored.
- Use aseptic technique and radiation shielding to withdraw Amyvid solution.
- Assay the dose in a suitable dose calibrator prior to administration.
- Inject Amyvid through a short intravenous catheter (approximately 1.5 inches or less) to minimize the potential for adsorption of the drug to the catheter. Portions of the Amyvid dose may adhere to longer catheters.

2.3 Image Acquisition Guidelines

A 10-minute PET image should be acquired starting 30 to 50 minutes after Amyvid intravenous injection. The patient should be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm.

2.4 Image Display and Interpretation

Amyvid images should be interpreted only by readers who successfully complete a special training program *[see Warnings and Precautions (5.1)]*. Training is provided by the manufacturer using either an in-person tutorial or an electronic process.

The objective of Amyvid image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of unique image features.

Image Display

Images should be displayed in the transaxial orientation with access as needed to the sagittal and coronal planes. In reviewing the images, include all transaxial slices of the brain using a black-white scale with the maximum intensity of the scale set to the maximum intensity of all the brain pixels. Initially locate the brain slice with the highest levels of image contrast (highest radioactivity signals for Amyvid uptake) and adjust the contrast appropriately. Start image interpretation by displaying slices sequentially from the bottom of the brain to the top. Periodically refer to the sagittal and coronal plane image display, as needed to better define the radioactivity uptake and to ensure that the entire brain is displayed.

Image Interpretation

Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of the image assessment *[see Warnings and Precautions (5.1)]*. Images are designated as positive or negative by comparing the radioactivity in cortical gray matter with activity in the adjacent white matter. This determination is made only in the cerebral cortex; the signal uptake in the cerebellum does not contribute to the scan interpretation (for example, a positive scan may show retained cerebellar gray-white contrast even when the cortical gray-white contrast is lost).

- *Negative scans* show more radioactivity in white matter than in gray matter, creating clear gray-white contrast.
- *Positive scans* show cortical areas with reduction or loss of the normally distinct gray-white contrast. These scans have one or more areas with increased cortical gray matter signal which results in reduced (or absent) gray-white contrast. Specifically, a positive scan will have either:
  a) Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent gray-white contrast. This is the most common appearance of a positive scan.
  or
  b) One or more areas in which gray matter radioactivity is intense and clearly exceeds radioactivity in adjacent white matter.

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortical ribbon, or image blur. For cases in which there is uncertainty as to the location or edge of gray matter on the PET scan and a co-registered computerized tomography (CT) image is available (as when the study is done on a PET/CT scanner) the interpreter should examine the CT image to clarify the relationship of the PET radioactivity and the gray matter anatomy.

Figures 1, 2, and 3 provide examples of negative and positive scans. Figure 1 demonstrates varying degrees of normal gray-white contrast (negative) and examples where gray-white contrast has been lost (positive). Figure 2 illustrates typical features of a negative scan, while Figure 3 shows the loss of gray-white contrast in different brain regions of a positive scan.

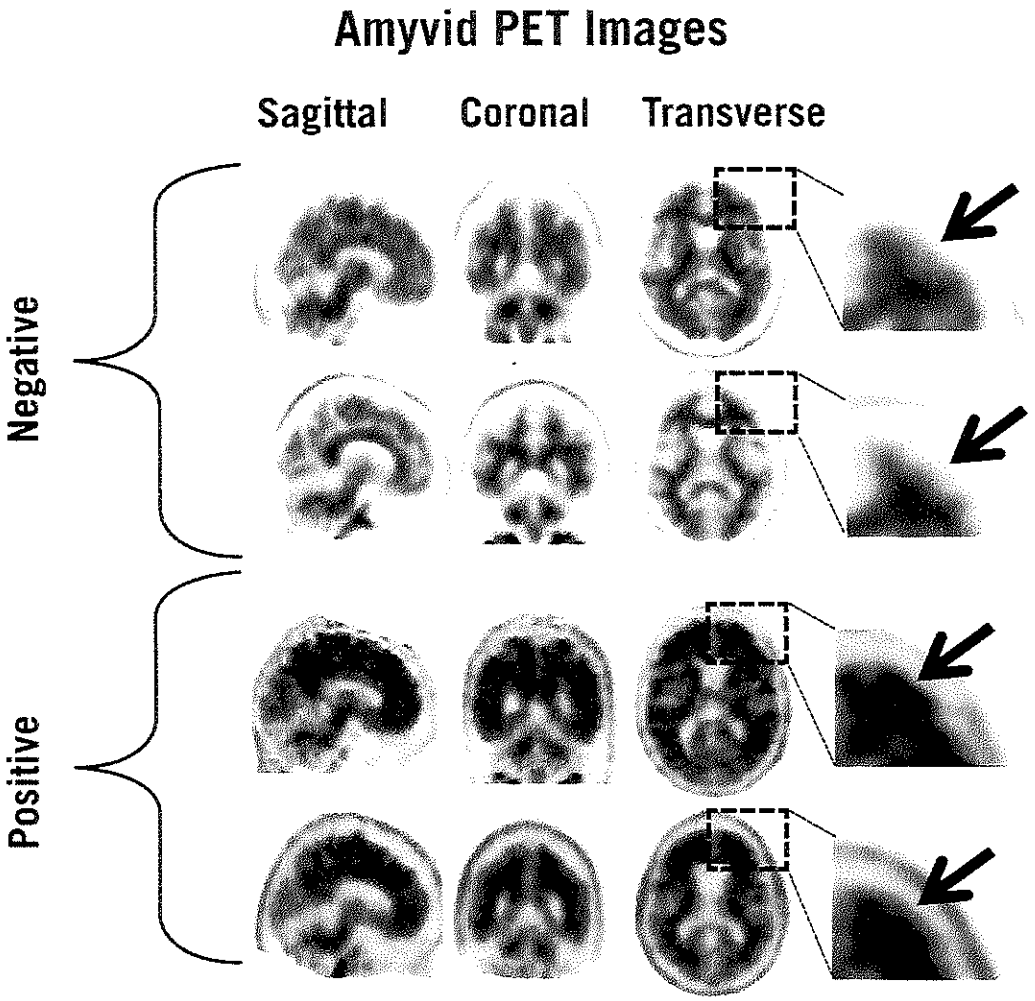


Figure 1: Examples of Amyvid negative scans (top two rows) and positive scans (bottom two rows). Left to right panels show sagittal, coronal, and transverse PET image slices. Final panel to right shows enlarged picture of the brain area under the box. The top two arrows are pointing to normal preserved gray-white contrast with the cortical radioactivity less than the adjacent white matter. The bottom two arrows indicate areas of decreased gray-white contrast with increased cortical radioactivity that is comparable to the radioactivity in the adjacent white matter.

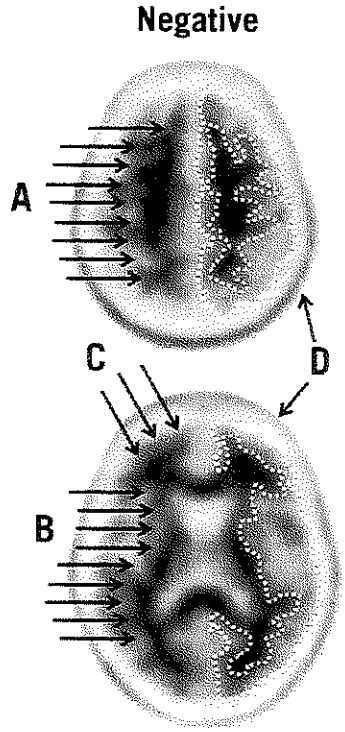


Figure 2: Typical Negative Scan. Images are displayed from a negative scan with upper (top) and lower (bottom) transverse slices both showing good gray-white matter contrast. On the right side of each slice, dotted lines have been used to illustrate the edge of the cortical gray matter (outer line) and the gray-white border (inner line). These dotted lines highlight contrast in uptake between the less intense uptake in the gray matter and the more intense uptake in the white matter. In addition, arrows illustrate the following points:

A) White matter tracts can be delineated from the frontal lobe to parietal lobe.

B) White matter tracts are clearly identified throughout the occipital / temporal area.

C) Scalloped appearance is seen with "fingers" of white matter in the frontal cortex.

D) Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.

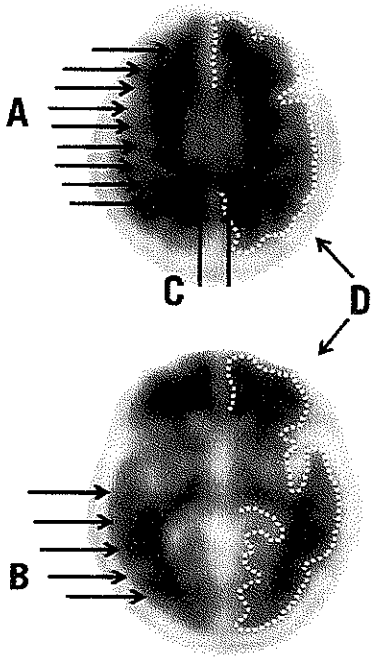


Figure 3: Typical Positive Scan: Images from a positive scan showing upper (top) and lower (bottom) transverse slices with loss of gray-white matter contrast in multiple brain regions. On the right side of each slice the edge of the cortical gray matter has been illustrated with a dotted line. Compared to the images from the negative case in Figure 2, the gray matter uptake is more similar to the white matter uptake and the gray-white matter border is more difficult to discern. In addition, arrows show the following points:

A) White matter tracts are difficult to fully identify as they travel from frontal to parietal lobe.

B) Borders of white matter tracts in occipital / temporal area are lost in places.

C) Gray matter in medial parietal cortex (precuneus) has increased uptake.

D) Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.

2.5 Radiation Dosimetry

The estimated radiation absorbed doses for adults from intravenous injection of Amyvid are shown in Table 1.

Table 1: Estimated Radiation Absorbed Dose, Amyvid (Florbetapir F 18 Injection)

ORGAN/TISSUE	MEAN ABSORBED DOSE PER UNIT ADMINISTERED ACTIVITY(μGy/MBq)
Adrenal	14
Bone - Osteogenic Cells	28
Bone - Red Marrow	14
Brain	10
Breasts	6
Gallbladder Wall	143
GI[a] - Lower Large Intestine Wall	28
GI - Small Intestine	66
GI - Stomach Wall	12
GI - Upper Large Intestine Wall	74
Heart Wall	13
Kidneys	14
Liver	64
Lungs	9
Muscle	9
Ovaries	18
Pancreas	14
Skin	6
Spleen	9
Testes	7
Thymus	7
Thyroid	7
Urinary Bladder Wall	27
Uterus	16
Total Body	12
Effective Dose (μSv/MBq)[b]	19

[a] Gastrointestinal

[b] Assumed radiation weighting factor, w_r, (formerly defined as quality factor, Q) of 1 for conversion of absorbed dose (Gray or rads) to dose equivalent (Sieverts or rem) for F 18. To obtain radiation absorbed dose in rad/mCi from above table, multiply the dose in μGy/MBq by 0.0037, (e.g., 14 μGy/MBq x 0.0037 = 0.0518 rad/mCi)

The effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.0 mSv in an adult. (19 x 370 = 7030 μSv = 7.030 mSv). The use of a CT scan to calculate attenuation correction for reconstruction of Amyvid images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent. The total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9 mSv.

3 DOSAGE FORMS AND STRENGTHS

Amyvid (Florbetapir F 18 Injection) is available in a 10 mL, 30 mL, and 50 mL multidose vial containing a clear, colorless solution at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis (EOS).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Image Misinterpretation and other Errors

Errors may occur in the Amyvid estimation of brain neuritic plaque density during image interpretation *[see Clinical Studies (14)]*.

Image interpretation should be performed independently of the patient's clinical information. The use of clinical information in the interpretation of Amyvid images has not been evaluated and may lead to errors. Other errors may be due to extensive brain atrophy that limits the ability to distinguish gray and white matter on the Amyvid scan as well as motion artifacts that distort the image.

Amyvid scan results are indicative of the brain neuritic amyloid plaque content only at the time of image acquisition and a negative scan result does not preclude the development of brain amyloid in the future.

5.2 Radiation Risk

Amyvid, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, 496 patients were exposed to Amyvid. Amyvid caused no serious adverse reactions in the studies and the reported adverse reactions were predominantly mild to moderate in severity. The adverse reactions reported in more than one subject within the studies are shown in Table 2.

Table 2: Adverse Reactions Reported in Clinical Trials (N=496 patients)

Adverse Reactions	N (Percent of patients)
Headache	9 (1.8%)
Musculoskeletal pain	4 (0.8%)
Fatigue	3 (0.6%)
Nausea	3 (0.6%)
Anxiety	2 (0.4%)
Back pain	2 (0.4%)
Blood pressure increased	2 (0.4%)
Claustrophobia	2 (0.4%)
Feeling cold	2 (0.4%)
Insomnia	2 (0.4%)
Neck pain	2 (0.4%)

7 DRUG INTERACTIONS

Pharmacodynamic drug-drug interaction studies have not been performed in patients to establish the extent, if any, to which concomitant medications may alter Amyvid image results.

Within a clinical study of patients with a range of cognitive impairment, some patients with probable AD were receiving the following medications: donepezil, galantamine, memantine. Mean cortical Standardized Uptake Value (SUV) ratios did not differ between the patients taking or not taking these concomitant medications. In *in vitro* tests, none of the drugs tested, including the acetylcholinesterase inhibitors donepezil, galantamine, and tacrine, altered florbetapir F 18 binding to its target.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. It is not known whether Amyvid can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted with Amyvid. Amyvid should be administered to a pregnant woman only if clearly needed.

All radiopharmaceuticals, including Amyvid, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the magnitude of the radiopharmaceutical dose. Assess pregnancy status before administering Amyvid to a female of reproductive potential.

8.3 Nursing Mothers

It is not known whether Amyvid is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for radiation exposure to nursing infants from Amyvid, avoid use of the drug in a breastfeeding mother or have the mother temporarily interrupt breastfeeding for 24 hours (>10 half-lives of radioactive decay for the F 18 isotope) after exposure to Amyvid. If breastfeeding is interrupted, the patient should pump and discard her breast milk and use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours after administration of the drug.

8.4 Pediatric Use

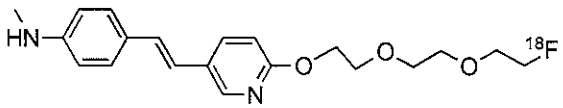
Amyvid is not indicated for use in pediatric patients.

8.5 Geriatric Use

Of 496 patients in completed clinical studies of Amyvid, 307 patients were ≥65 years old (203 patients were over 75 years of age). No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

Amyvid contains florbetapir F 18, a molecular imaging agent that binds to β-amyloid aggregates, and is intended for use with PET imaging of the brain. Chemically, florbetapir F 18 is described as (E)-4-(2-(6-(2-(2-(2[^{18}F] fluoroethoxy)ethoxy)ethoxy)pyridine-3-yl)vinyl)-N-methylbenzamine. The molecular weight is 359 and the structural formula is:



Amyvid is a sterile, non-pyrogenic radioactive diagnostic agent for intravenous injection. The clear, colorless solution is supplied ready to use and each milliliter contains 0.1 to 19 micrograms of florbetapir and 500 - 1900 MBq (13.5 - 51 mCi) florbetapir F 18 at EOS, 4.5 mg sodium ascorbate USP and 0.1 mL dehydrated alcohol USP in 0.9% sodium chloride injection USP. The pH of the solution is between 5.5 and 7.5.

11.1 Physical Characteristics

Amyvid is radiolabeled with [^{18}F] fluorine (F 18) that decays by positron (β^+) emission to O 18 and has a half-life of 109.77 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 3).

Table 3: Principal Radiation Produced from Decay of Fluorine 18

Radiation	Energy Level (keV)	Abundance (%)
Positron	249.8	96.9
Gamma	511	193.5

11.2 External Radiation

The point source air-kerma coefficient[a] for F-18 is 3.74E -17 Gy m^2/(Bq s); this coefficient was formerly defined as the specific gamma-ray constant of 5.7 R/hr/mCi at 1 cm. The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm[b]. The relative reduction of radiation emitted by F-18 that results from various thicknesses of lead shielding is shown in Table 4. The use of ~8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 4: Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

[a] Eckerman KF and A Endo. MIRD: Radionuclide Data and Decay Schemes, 2nd Edition, 2008.
[b] Derived from data in NCRP Report No. 49. 1998, Appendix C

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Florbetapir F 18 binds to β-amyloid plaques and the F 18 isotope produces a positron signal that is detected by a PET scanner. In *in vitro* binding studies using postmortem human brain homogenates containing β-amyloid plaques, the dissociation constant (K_d) for florbetapir was 3.7 ± 0.3 nM. The binding of florbetapir F 18 to β-amyloid aggregates was demonstrated in postmortem human brain sections using autoradiographic methods, thioflavin S and traditional silver staining correlation studies as well as monoclonal antibody β-amyloid-specific correlation studies. Florbetapir binding to tau protein and a battery of neuroreceptors was not detected in *in vitro* studies.

12.2 Pharmacodynamics

Following intravenous injection, florbetapir F 18 diffuses across the human blood-brain barrier and produces a radioactivity signal detectable throughout the brain. Subsequently, cerebral perfusion decreases the brain florbetapir F 18 content, with differential retention of the drug in areas that contain β-amyloid aggregates compared to areas that lack the aggregates. The time-activity curves for florbetapir F 18 in the brain of subjects with positive scans show continual signal increases from time zero through 30 minutes post-administration, with stable values thereafter up to at least 90 minutes post-injection. Differences in the signal intensity between portions of the brain that specifically retain florbetapir F 18 and the portions of the brain with nonspecific retention of the drug forms the image interpretation methods *[see Dosage and Administration (2.5)]*.

Clinical studies evaluated the test-retest distribution of florbetapir F 18 within the brains of 21 subjects (11 with probable AD and 10 healthy volunteers) who underwent two injections (with PET scans), separated by a time period of 2 to 30 days. Images were shown to maintain signal distribution reproducibility when evaluated qualitatively (by a reader masked to image time points) as well as quantitatively using an automated assessment of SUV in pre-specified brain regions. A comparison of a 10-minute image acquisition time versus a 20-minute acquisition time showed no difference in the mean cortical to cerebellar SUV ratio results obtained.

12.3 Pharmacokinetics

Following the intravenous administration of 370 MBq (10 mCi) of florbetapir F 18 to healthy volunteers, the drug was distributed throughout the body with less than 5% of the injected F 18 radioactivity present in the blood by 20 minutes following administration, and less than 2% present by 45 minutes after administration. The residual F 18 in circulation during the 30-90 minute imaging window was principally in the form of polar F 18 metabolites. Whole body scanning following the intravenous injection showed accumulation of radioactivity in the liver within four minutes post-injection, followed by elimination of the radioactivity predominantly through the biliary/gastrointestinal tract with much lower radioactivity detected in the bladder. Essentially all radioactivity collected in the urine was present as polar metabolites of florbetapir F 18.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies to assess the carcinogenicity or reproductive toxicity potentials of Amyvid have not been conducted.

In an *in vitro* bacterial reverse mutation assay (Ames test), increases in the number of revertant colonies were observed in 2 of the 5 strains exposed to ^{19}F-AV-45, the non-radioactive form of florbetapir F 18. In a chromosomal aberration *in vitro* study with cultured human peripheral lymphocytes, ^{19}F-AV-45 did not increase the percentage of cells with structural aberrations with 3-hour exposure with or without activation; however, 22-hour exposure produced a statistically significant increase in structural aberrations at all tested concentrations. Potential *in vivo* genotoxicity of ^{19}F-AV-45 was evaluated in a mouse micronucleus study. In this assay, ^{19}F-AV-45 did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level, 372 µg/kg/day, when given twice daily for 3 consecutive days.

14 CLINICAL STUDIES

Amyvid was evaluated in three clinical studies that examined images from healthy adult subjects as well as subjects with a range of cognitive disorders, including some terminally ill patients who had agreed to participate in a postmortem brain donation program. All the studies were single arm studies in which subjects underwent an Amyvid injection and scan and then had images interpreted by multiple independent readers who were masked to all clinical information. Image interpretations used co-registration with CT scans when PET scans were performed on dual PET-CT scanners.

In Study One, a semi-quantitative Amyvid image interpretation method, which is not intended for clinical use, was used by three readers to interpret images from 152 terminally ill patients, of whom 35 underwent autopsy (29 included in primary analysis). The median patient age was 85 years (range 55 to 103 years) and 14 of the patients were female. Eighteen of the patients had dementia, 9 had no cognitive impairment and 2 had mild cognitive impairment (MCI). The main study outcome was a comparison of premortem Amyvid images to the findings from a postmortem brain examination (truth standard). The semi-quantitative measures consisted of a five-point whole brain Amyvid uptake image scoring outcome that was compared to a global score of the percentage of the whole brain that contained amyloid, as determined by immunohistochemical microscopy. The percentage of postmortem cortical amyloid burden ranged from 0 to 9% and correlated with the median Amyvid scores (Spearman's rho=0.78; $p<0.0001$, 95% CI, 0.58 to 0.89).

Studies Two and Three used a clinically-applicable binary image interpretation method (positive/negative) to evaluate images from a range of patients who had participated in earlier studies. The studies assessed performance characteristics (sensitivity and specificity) among subjects with a postmortem amyloid neuritic plaque density truth standard. Additionally, inter-reader and intra-reader image interpretation reproducibility was assessed among all the subjects, including subjects who lacked a postmortem truth standard. Before image interpretation, all readers underwent special training: Study Two used an in-person tutoring type of training and Study Three used an electronic media-based training method. Five trained readers interpreted images independently within each study. The brain neuritic plaque density in both studies was determined using an algorithm in which microscopic measures of highest plaque density within a brain region were averaged to produce a global brain estimate of neuritic plaque density. The global neuritic plaque density was categorized in the same manner as that for a region (Table 5), where plaques were counted on slides with modified Bielschowsky silver stained tissue sections. For purposes of determining the agreement between the in-vivo Amyvid image results and the post-mortem whole brain amyloid neuritic plaque density, Amyvid results (negative/positive) were pre-specified to correspond

with specific plaque density scores, based upon a modification of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria which use neuritic plaque counts as a necessary pathological feature of AD.

Table 5: Global and Regional Neuritic Plaque Density[a] Correlates to Amyvid Image Results

Neuritic Plaque Counts	CERAD Score	Amyvid Image Result
<1	none	Negative
1 - 5	sparse	
6 - 19	moderate	Positive
20+	frequent	

[a] J of Neuropathology and Experimental Neurology 1997; 56(10):1095.

Study Two examined images only from terminally ill patients who had premortem Amyvid scans and postmortem brain examinations to determine a truth standard. Among the 59 patients, 35 of whom were also in Study One, the median age was 83 years (range 47 to 103 years), half were females and most were Caucasian (93%). Twenty-nine patients had an AD clinical diagnosis, 13 had another type of dementing disorder, 12 had no history of cognitive impairment and 5 had MCI. The time interval between the Amyvid scan and death was less than one year for 46 patients and between one and two years for 13 patients. Among the subset of patients who died within one year of Amyvid scanning (a prespecified outcome), the sensitivity using the majority interpretation of the readers was 96% (95% CI: 80% to 100%) and specificity was 100% (95% CI: 78% to 100%). With the entire dataset of 59 patients, the sensitivity using the majority interpretation of the readers was 92% (95% CI: 78% to 98%) and specificity was 100% (95% CI: 80% to 100%). At autopsy, the global brain neuritic plaque density category (CERAD score, as in Table 5) was: frequent n=30; moderate n=9; sparse n=5; and none n=15. Tables 6 and 7 show the Amyvid performance characteristics among all the patients. Among the subset of patients who died within one year of Amyvid scanning (n=46; 28 positive and 18 negative based on histopathology) the median (and range) of correct read results, false negatives, and false positives were 44 (37 to 45), 1 (0 to 7), and 1 (0 to 2), respectively, for In-Person Training (Study Two); and were 43 (38 to 44), 3 (0 to 7), and 1 (0 to 2), respectively, for Electronic Media Training (Study Three).

Table 6: Amyvid Scan Results by Reader Training Method among Autopsied Patients (n = 59)

Test Performance		In-Person Training (Study Two)	Electronic Media Training (Study Three)
Sensitivity (%)	Median	92	82
	Range among the 5 readers	(69 – 95)	(69 – 92)
Specificity (%)	Median	95	95
	Range among the 5 readers	(90 – 100)	(90 – 95)

Table 7: Amyvid Correct and Erroneous Scan Results by Reader Training Method among Autopsied Patients

Read Result		In-Person Training (Study Two)					Electronic Media Training (Study Three)				
		Reader					Reader				
		1	2	3	4	5	6	7	8	9	10
All Scans with Autopsies (N=59[a])	Correct	55	56	53	56	45	49	54	46	53	51
	False Negative	3	2	5	3	12	8	3	12	5	7
	False Positive	1	1	1	0	2	2	2	1	1	1

[a] 39 positive and 20 negative based on histopathology

Study Three included images from subjects who did not have a truth standard (20 healthy volunteers, 52 patients with mild cognitive impairment, 20 patients with AD) as well as all 59 of the patients who underwent an autopsy (same patients as in Study Two) and provided a truth standard. Duplicate images of 33 patients were included within the total pool of images in order to assess intra-reader image reproducibility. Among the 151 subjects, the median age was 76 years (range 47 to 103), half were females and most were Caucasian (93.4%). Performance characteristics for patients with a truth standard are shown above (Tables 6 and 7). The major reproducibility results are shown in Table 8 for various groups of subjects. Inter-reader reproducibility analyses for all images showed an overall Fleiss' kappa statistic of 0.83 (95% CI: 0.78 to 0.88); the lower bound of the 95% CI exceeded the pre-specified success criterion (95% CI lower bound >0.58). Intra-reader reproducibility analyses showed that, between the two readings for each of the 33 patients with duplicate images, one of the five readers had complete agreement for all 33 patients, two readers had discrepant reads for a single patient, one reader had discrepant reads for two patients and another reader had discrepant reads for three patients.

Table 8: Number of Positive Amyvid Scan Results within Study Three Subject Groups and Reproducibility of Scan Results Among Readers

Subject group by cognitive and truth standard (TS, autopsy) status	Positive Scans, n[a]	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agree	4 of 5 readers agree	5 of 5 readers agree
All subjects with a TS, n=59	33	0.75 (0.67, 0.83)	14	10	76
All subjects without a TS, n=92	33	0.88 (0.82, 0.94)	2	11	87
AD, n=49 (29 with TS; 20 no TS)	38	0.67 (0.58, 0.76)	10	14	76
MCI, n=57 (5 with TS; 52 no TS)	17	0.91 (0.83, 0.99)	2	7	91
Cognitively normal without TS, n=20	4	0.83 (0.69, 0.97)	5	5	90
Cognitively normal with TS, n = 12	1	0.73 (0.55, 0.87)	0	8	92
Other (non-AD) dementia with TS, n = 13	7	0.52 (0.35, 0.69)	23	23	54

[a] Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of patients listed in the first column.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Amyvid is supplied in 10 mL, 30 mL, or 50 mL vials containing 10 mL, 10-30 mL, or 10-50 mL, respectively, of a clear, colorless solution at a strength of 500 - 1900 MBq/mL (13.5 - 51 mCi/mL) florbetapir F 18 at EOS. Each vial contains multiple doses and is enclosed in a shielded container to minimize external radiation exposure.

10 mL	NDC 0002-1200-10 (IC1200)
30 mL	NDC 0002-1200-30 (IC1200)
50 mL	NDC 0002-1200-50 (IC1200)

16.2 Storage and Handling

Store Amyvid at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. The product does not contain a preservative. Store Amyvid within the original container or equivalent radiation shielding. Amyvid must not be diluted.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

- Instruct patients to inform their physician or healthcare provider if they are pregnant or breastfeeding.
- Inform patients who are breastfeeding to use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours (>10 half-lives of radioactive decay for the F 18 isotope) after administration of the drug or avoid use of the drug.

Marketed by Lilly USA, LLC, Indianapolis, IN 46285, USA

PV 9200 AMP

Bulk Drug Product Vial Label

NDC Code 0002-1200-30[1]
Amyvid™
Florbetapir F 18 Injection

Sterile
Rx Only

CAUTION: RADIOACTIVE MATERIAL

Batch No:_____Date:_____

For Intravenous Use.
Contains 0.1 to 19 micrograms of florbetapir and 500 – 1900 MBq (13.5 - 51 mCi) florbetapir F 18 at end of synthesis (EOS), 4.5 mg sodium ascorbate USP and 0.1 mL dehydrated alcohol USP in 0.9% sodium chloride injection USP per milliliter of solution. Store at USP controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Manufactured by "Contract Manufacturing Organization"[2] for Avid Radiopharmaceuticals, a wholly-owned subsidiary of Eli Lilly and Company, Philadelphia, PA 19104

[1]Other vial sizes will have NDC Codes: 0002-1200-10 or 0002-1200-50
[2]PETNET Solutions, Inc. Knoxville, TN 37932 or Cardinal Health 414, LLC, Dublin, OH 43017 depending on manufacturing facility.

Bulk Drug Product Shield Label

NDC Code 0002-1200-30[1]
Amyvid™
Florbetapir F 18 Injection

Sterile
Rx Only

CAUTION: RADIOACTIVE MATERIAL

_____MBq (_____mCi) in _____ mL at ____:____ on _____

Batch No._____

For Intravenous Use.
Contains 0.1 to 19 micrograms of florbetapir, 4.5 mg sodium ascorbate USP and 0.1 mL dehydrated alcohol USP in 0.9% sodium chloride injection USP per milliliter of solution.
Store at USP controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Expires at ____:____ on _____

Manufactured by "Contract Manufacturing Organization"[2] for Avid Radiopharmaceuticals, a wholly-owned subsidiary of Eli Lilly and Company, Philadelphia, PA 19104

[1]Other vial sizes will have NDC Codes: 0002-1200-10 or 0002-1200-50
[2]PETNET Solutions, Inc. Knoxville, TN 37932 or Cardinal Health 414, LLC, Dublin, OH 43017 depending on manufacturing facility.

IRB NUMBER: 2017-471
IRB APPROVAL DATE: 01/10/2020

Hachinski Ischemic Scale

Study ID ___ ___ ___ ___ ___ ___ ___

Rater _____

Date ___/___/___

This form to be completed by the clinician.

Circle only one number per characteristic

HACHINSKI ISCHEMIC SCORE[1]		
Please complete the following scale using information obtained from history/physical/neurological exam and/or medical records. Indicate if a characteristic is present or characteristic of the patient by circling the appropriate value		
	Present	**Absent**
1. Abrupt onset (re: cognitive status)	2	0
2. Stepwise deterioration (re: cognitive status)	1	0
3. Somatic complaints	1	0
4. Emotional incontinence	1	0
5. History of presence of hypertension	1	0
6. History of stroke	2	0
7. Focal neurological symptoms	2	0
8. Focal neurological signs	2	0

9. Sum all circled answers for a Total Score: ____

[1] Rosen Modification of Hachinski Ischemic Score (An Neurol 7:486-488. 1980).

(Version 1.2, March 2006)