ELSEVIER

Alzheimer's & Dementia 6 (2010) 239–246

Alzheimer's & Dementia

Clinical core of the Alzheimer's disease neuroimaging initiative: Progress and plans

Paul S. Aisen[a,*], Ronald C. Petersen[b], Michael C. Donohue[c], Anthony Gamst[c], Rema Raman[c], Ronald G. Thomas[c], Sarah Walter[a], John Q. Trojanowski[d], Leslie M. Shaw[d], Laurel A. Beckett[e], Clifford R. Jack, Jr.[f] William Jagust[g], Arthur W. Toga[h], Andrew J. Saykin[i], John C. Morris[j], Robert C. Green[k], Michael W. Weiner;[l] and the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Neurosciences, University of California San Diego, CA, USA*
[b]*Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN, USA*
[c]*Division of Biostatistics and Bioinformatics, University of California, San Diego, San Diego, CA, USA*
[d]*Department of Pathology & Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[e]*Department of Public Health Sciences, University of California Davis*
[f]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[g]*Helen Wills Neuroscience Institute, University of California, Berkeley CA*
[h]*Laboratory of Neuroimaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA*
[i]*Department of Radiology, Indiana University, Indianapolis, IN, USA*
[j]*Department of Neurology, Washington University School of Medicine, St. Louis, MI, USA*
[k]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[l]*Department of Radiology, and Medicine and Psychiatry, UC San Francisco, San Francisco, CA, USA*

Abstract The Clinical Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI) has provided clinical, operational, and data management support to ADNI since its inception. This article reviews the activities and accomplishments of the core in support of ADNI aims. These include the enrollment and follow-up of more than 800 subjects in the three original cohorts: healthy controls, amnestic mild cognitive impairment (now referred to as late MCI, or LMCI), and mild Alzheimer's disease (AD) in the first phase of ADNI (ADNI 1), with baseline longitudinal, clinical, and cognitive assessments. These data, when combined with genetic, neuroimaging, and cerebrospinal fluid measures, have provided important insights into the neurobiology of the AD spectrum. Furthermore, these data have facilitated the development of novel clinical trial designs. ADNI has recently been extended with funding from an NIH Grand Opportunities (GO) award, and the new ADNI GO phase has been launched; this includes the enrollment of a new cohort, called early MCI, with milder episodic memory impairment than the LMCI group. An application for a further 5 years of ADNI funding (ADNI 2) was recently submitted. This funding would support ongoing follow-up of the original ADNI 1 and ADNI GO cohorts, as well as additional recruitment into all categories. The resulting data would provide valuable data on the earliest stages of AD, and support the development of interventions in these critically important populations.

Keywords: Alzheimer's disease; ADNI; Clinical trials

1. Introduction

The goals of the Alzheimer's Disease Neuroimaging Initiative (ADNI) are accomplished through the enrollment and longitudinal follow-up of cohorts of individuals with

*Corresponding author. Tel.: 858-622-2028; Fax: 858-246-0138.
E-mail address: paisen@ucsd.edu

1552-5260/$ – see front matter
doi:10.1016/j.jalz.2010.03.006

mild cognitive impairment (MCI) and mild Alzheimer's disease (AD), as well as cognitively normal older individuals. These ADNI subjects were selected on the basis of specific criteria and enrolled at the 57 ADNI performance sites in North America. They are followed up with medical evaluations, clinical, cognitive, functional, and behavioral assessments. In addition, they undergo biochemical biomarker, structural and functional neuroimaging, and genetic assessments under the guidance of the ADNI biomarker; magnetic resonance resonance (MRI) and positron emission tomography (PET); and genetics cores, respectively.

The ADNI Clinical Core is responsible for operational and data management aspects of the study, including subject recruitment, retention, and assessment activities at all sites. Core activities also include development of the protocol and procedures manuals, regulatory oversight, maintenance of the ADNI network of performance sites, monitoring of site staffing, recruitment, compliance and data entry, financial subcontracting, study supply management, and development and maintenance of the ADNI data system in accordance with the aims of the program and the ADNI executive committee. The clinical core also manages the process of adjudicating conversion of subjects from one diagnostic category to another.

The first funding cycle of ADNI (referred to as ADNI 1) supported the recruitment of 400 individuals with amnestic MCI according to the Petersen criteria as operationalized by the Alzheimer's Disease Cooperative Study, along with 200 cognitively normal older individuals and 200 with mild AD [1]. Toward the end of 2009, ADNI was awarded additional support, in the form of a Grand Opportunities (GO) grant, from the National Institute on Aging for a 2-year period to allow further longitudinal follow-up, imaging, and data analysis for the ADNI 1 cohorts, as well as the recruitment of a fourth cohort of less impaired individuals with MCI. The phase of study funded by this award is referred to as ADNI GO. At approximately the same time, an application was submitted to NIH by the ADNI investigators requesting a 5-year extension of ADNI, referred to as ADNI 2.

This report, adapted from the ADNI 2 grant application, summarizes progress of the ADNI Clinical Core, including the proposed activities for ADNI 2.

2. Background and overview of ADNI Clinical Core

Currently, no therapies are available for AD that alter the underlying nature of the disease process. Fortunately, there are more than 100 compounds under investigation by various pharmaceutical companies and university medical centers around the world. Most of these therapies are designed to have an effect on the underlying disease process itself. The earlier the intervention takes place, presumably, the greater the protection against further neuronal damage will be appreciated.

ADNI has established pre-competitive collaboration and real-time data sharing among academia and industry investigators to clarify the relationships among demographic, genetic, clinical, cognitive, neuroimaging, and biochemical measures throughout the course of AD neurobiology to facilitate the development of effective therapeutics. The project has provided insights into disease mechanisms, and has provided guidance to drug development programs based primarily on the use of standardized biomarkers. ADNI has increased the rate of drug development; disease-modifying therapies will arrive in the clinic sooner. Many leading disease-modifying drug development programs are now using ADNI methodology toward more efficient trial design, particularly in the critically important early (pre-dementia) AD population.

AD can be diagnosed with reasonable accuracy at the dementia stage. In fact, a recent evidence-based medicine review of the published data by the American Academy of Neurology documented that clinicians were quite accurate when the clinical diagnoses were subsequently compared with neuropathologic findings [2]. However, as one identifies the disease process at an earlier point in the clinical continuum, the precision of the diagnosis is reduced. An important challenge is to try to identify the process at the pre-dementia stage and enhance the specificity of the clinical diagnosis through the use of imaging and other biomarkers. This approach assumes an underlying cascade of pathological events that lend themselves to intervention [3,4]. Biochemical and neuroimaging biomarkers can provide a window on the

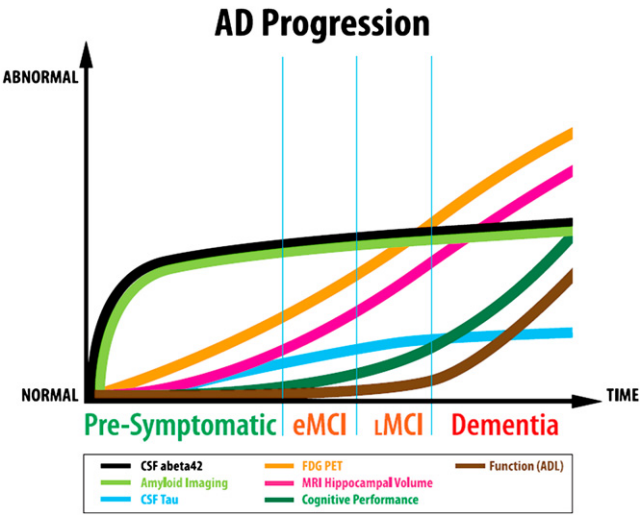

Fig. 1. Trajectories of biomarkers during the progression of AD. This hypothetical graph is designed to capture the following points: (1) CSF $A\beta_{42}$ and amyloid PET, reflecting amyloid accumulation in brain, move in tandem. (2) Amyloid accumulation precedes cognitive and functional decline by years, and changes only gradually after symptoms develop. (3) Compared to CSF $A\beta_{42}$ and amyloid PET, CSF tau, MRI volumes, and FDG-PET are more dynamic biomarkers of disease progression across the spectrum of AD neurobiology. (4) Cognitive decline becomes evident at the onset of EMCI, and accelerates as the disease progresses. (5) Functional decline becomes evident at the onset of dementia, and accelerates as the disease progresses. (6) All of these points are conjectural to varying degrees; they require confirmation with long-term longitudinal follow-up in ADNI 2 and beyond [Modified from Lancet Neurol 2010;9:119–28, with permission.]

underlying neurobiology, facilitating early identification and intervention. In Fig. 1, a hypothetical model of the trajectories of biomarkers that have been studied in ADNI 1 is seen, which will continue to be followed up longitudinally during the continuation of ADNI [3]. To test this model, it is essential to acquire very long-term longitudinal follow-up; the ADNI 2 proposal covers up to a decade of follow-up of the original ADNI 1 subjects. As is indicated in Fig. 1, there is evidence that the accumulation of $A\beta_{42}$ (presumed by some investigators to be the molecular trigger in AD neurodegeneration) occurs early in the process. This can be detected by molecular imaging techniques such as PET scanning using an amyloid-specific ligand or through measurement of cerebrospinal fluid (CSF) $A\beta_{42}$. The next event involves neuronal injury and dysfunction which may be detected by fluorodeoxyglucose (FDG)-PET measures of regional metabolic activity, elevated levels of CSF tau indicating neuronal damage, phospho-tau indicating accumulating tangle pathology, and MRI volumetric changes. When a threshold of neuronal dysfunction is reached, cognitive and then functional manifestations of AD accelerate. However, as mentioned earlier, by this point in the continuum, it is likely that considerable damage has occurred in the central nervous system, and some of this may be irreversible. Consequently, most investigators believe that early intervention is preferable to waiting to treat individuals when the full dementia syndrome is present.

As shown in Fig. 1, amyloid biomarker abnormalities are present during the asymptomatic stage. Ideally, one would like to intervene at this point to have the greatest effect on subsequent neuronal damage. However, there is a tremendous challenge to identifying subjects at risk with sufficient sensitivity and specificity in the asymptomatic stage to allow intervention at this point. ADNI 2 will address the role of neuroimaging and other biomarkers at the stage of early clinical symptom presentation (early MCI, or EMCI). Ultimately, it may be feasible to move diagnosis and intervention into the asymptomatic stage.

ADNI 1 has focused on subjects with amnestic mild cognitive impairment (aMCI). The construct of MCI has been extensively evaluated around the world, and thousands of studies have been completed in the past decade [5]. Although all these studies are not entirely consistent, the wealth of the data coalesces to indicate that an aMCI is an identifiable entity with a predictable progression to clinical dementia [6]. However, data to be reviewed later from ADNI 1 indicate that significant structural and functional imaging changes as well as chemical biomarker profiles are evident at the MCI stage as defined in ADNI 1 [1].

In ADNI GO and ADNI 2, we will study a group of subjects with less severe memory impairment than found in the MCI cohort enrolled in ADNI 1. It is important to emphasize that these subjects will still meet criteria for aMCI, but they will be at an earlier point in the clinical spectrum. With funding from the National Institute on Aging through the GO grant, we will be recruiting 200 EMCI between 2009 and 2011. In ADNI 2, we propose to continue to follow-up these EMCI subjects, along with 202 subjects who are cognitively normal and 274 subjects who have late MCI (LMCI) (as defined in ADNI 1) going forward. In addition, we will recruit new cohorts of 150 cognitively normal subjects, 100 additional EMCI subjects, 150 LMCI subjects, and 150 subjects with mild AD. Thus, ADNI 2 combines these newly recruited subjects with those recruited in ADNI 1 and ADNI GO.

ADNI 1 clearly established the utility of ^{11}C -Pittsburgh Compound B (PIB) amyloid imaging; ADNI GO and ADNI 2 (if funded) will examine the more widely feasible ^{18}F amyloid imaging (AV-45). ADNI 2 will confirm and extend the striking findings linking regional brain volumes (e.g, hippocampal volume, regional cortical thickness) to AD progression, providing a potential selection criterion, covariate or outcome measure for trials, as well as the utility of functional brain measures by FDG-PET. The striking correspondence between CSF $A\beta_{42}$ and amyloid imaging will be confirmed and extended to the EMCI population. The utility of measures appropriate to primary care settings for the screening and selection of mildly impaired subjects will be assessed.

The primary purpose of this ongoing work is to continue to elucidate disease mechanisms, improve the efficiency of trial designs, and characterize a very early stage of disease (EMCI), which may be optimal for disease-modification interventions.

The ADNI Clinical Core facilitated the accomplishment of the ADNI aims, including the recruitment and retention of more than 800 subjects (229 normals, 380 LMCI, 210 AD), retention of subjects with an annual attrition rate of only 6%, electronic data capture, quality control and

Table 1
Baseline characterization of ADNI 1 cohorts

Characteristic	Controls (n = 229)	MCI (n = 398)	Mild AD (n = 192)
Age, mean ± SD, yr	75.8 ± 5.0	74.7 ± 7.4	75.3 ± 7.5
Education, mean ± SD, yr	16.0 ± 2.9	15.7 ± 3.0	14.7 ± 3.1
Sex (% Female)	48.0	35.4	47.4
Apolipoprotein E ε4, % carriers	26.6	53.3	66.1
MMSE Score	29.1 ± 1.0	27.0 ± 1.8	23.3 ± 2.1
CDR Global Score	0.0 ± 0.0	0.5 ± 0.0	0.7 ± 0.3
CDR Sum of Boxes	0.0 ± 0.1	1.6 ± 0.9	4.3 ± 1.6
GDS Score	0.8 ± 1.1	1.6 ± 1.4	1.7 ± 1.4
ADCS MCI-ADL (FAQ) Score	0.1 ± 0.6	3.9 ± 4.5	13.0 ± 6.9
ADAS-cog total	6.2 ± 2.9	11.5 ± 4.4	18.6 ± 6.3
ADAS word list delayed recall	2.9 ± 1.7	6.2 ± 2.3	8.6 ± 1.6
AVLT Trials 1–5	43.3 ± 9.1	30.7 ± 9.0	23.2 ± 7.7
AVLT delayed recall	7.4 ± 3.7	2.8 ± 3.3	0.7 ± 1.6
AVLT DR/Trial 5%	65.8 ± 27.6	32.1 ± 31.3	11.2 ± 22.0
Trails A (s)	36.5 ± 13.2	44.9 ± 22.8	68.0 ± 36.9
Trails B (s)	89.2 ± 44.3	130.7 ± 73.5	198.9 ± 87.2
Category fluency (animal)	19.9 ± 5.6	15.9 ± 4.9	12.4 ± 4.9
Category fluency (vegetable)	14.7 ± 3.9	10.7 ± 3.5	7.8 ± 3.3
Number cancellation	0.4 ± 0.7	1.0 ± 0.9	1.8 ± 1.3
Boston naming test	27.9 ± 2.3	25.5 ± 4.1	22.4 ± 6.2
Digits backwards	7.2 ± 2.2	6.2 ± 2.0	5.0 ± 1.8
Clock drawing	4.7 ± 0.7	4.2 ± 1.0	3.4 ± 1.3

Table 2
Annual change in cognitive and clinical assessment scores for ADNI 1 cohorts

	Controls	MCI	Mild AD
Assessment	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)
MMSE Score	0.0 ± 1.4 (211)	−0.7 ± 2.5 (358)	−2.4 ± 4.1 (162)
CDR Global Score	0.0 ± 0.1 (207)	0.0 ± 0.2 (358)	0.3 ± 0.5 (160)
CDR Sum of Boxes	0.1 ± 0.3 (207)	0.6 ± 1.2 (358)	1.6 ± 2.2 (160)
GDS Score	0.2 ± 1.2 (211)	0.4 ± 1.8 (358)	0.3 ± 1.8 (159)
ADCS MCI-ADL (FAQ) Score	0.1 ± 1.0 (210)	1.9 ± 4.0 (354)	4.6 ± 5.6 (161)
ADAS-cog total	−0.5 ± 3.0 (210)	1.1 ± 4.4 (357)	4.3 ± 6.6 (161)
AVLT Trials 1–5	0.2 ± 7.8 (209)	−1.3 ± 6.3 (357)	−3.6 ± 5.7 (156)
AVLT delayed recall	0.4 ± 3.4 (210)	−0.4 ± 2.4 (358)	−0.5 ± 1.6 (155)
AVLT DR/Trial 5%	4.9 ± 43.7 (209)	−5.0 ± 28.3 (353)	−7.1 ± 21.0 (147)
Trails A (seconds)	−2.3 ± 11.2 (211)	1.2 ± 16.1 (358)	3.9 ± 21.7 (157)
Trails B (seconds)	−6.6 ± 38.0 (210)	9.0 ± 56.1 (352)	20.0 ± 85.6 (133)
Category fluency (animal)	0.5 ± 4.6 (211)	−0.7 ± 4.4 (358)	−1.5 ± 4.0 (160)
Category fluency (vegetable)	−0.1 ± 3.5 (211)	−0.6 ± 3.1 (358)	−1.0 ± 2.8 (160)
Number cancellation	0.0 ± 0.7 (209)	−0.1 ± 0.9 (354)	0.3 ± 1.4 (155)
Boston naming test	0.5 ± 1.7 (210)	−0.2 ± 2.9 (356)	−1.5 ± 3.7 (159)
Digits backwards	0.1 ± 1.9 (211)	−0.3 ± 1.7 (356)	−0.2 ± 1.7 (152)
Clock drawing	0.0 ± 0.8 (211)	−0.1 ± 1.0 (357)	−0.4 ± 1.3 (162)

reporting, and coordination of FDG-PET, ^{11}C PIB PET, 1.5T MRI, 3T MRI, and CSF biomarkers. It has also initiated the ADNI GO project, which will include the recruitment and follow-up of an additional 200 subjects with EMCI. The ADNI Clinical Core infrastructure uses the Alzheimer's Disease Cooperative Study Administrative, Clinical Operations, Medical and Data Cores, all located at the University of California San Diego.

A novel feature of ADNI is public data access. Immediately after completion of processing and quality control procedures, ADNI data are placed on a public website that is available to any qualified investigator worldwide. Thus far, the data have been accessed by thousands of investigators and dozens of pharmaceutical firms.

3. Clinical core progress: ADNI 1 subjects

ADNI 1 began enrollment in late 2005 and completed enrollment of 819 subjects in 2007. Fifty-seven sites in the United States and Canada participated in the enrollment. Details of the inclusion criteria, recruitment, and baseline characterization of the ADNI 1 cohorts have been recently reported [1]. Key characteristics are shown in Table 1. The annual change scores on key cognitive and clinical assessments of subjects in the three clinical groups over the course of 12 months are shown in Table 2. Of particular note, 16% of the MCI subjects in ADNI 1 converted to AD in the first 12 months, and an additional 24% converted in the second year.

4. Clinical trial design progress

The real-time, public sharing of ADNI demographic, clinical, cognitive, and biomarker data has facilitated clinical trial design in academic and industry programs world-wide.

The great majority of AD drug development programs focus on symptomatic and disease-slowing effects in subjects with AD dementia [7]. The most widely-used co-primary outcome measures for such trials are the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) for cognition and the Clinical Dementia Rating scale sum-of-boxes (CDR-SB) for clinical status. The Neuropsychiatric Inventory is the standard measure of behavioral symptoms. Each of these measures is part of the assessment battery of ADNI. Therefore, trialists can and do use the shared ADNI data to explore the relationships among demographic parameters and performance on these measures, can explore analytical methods and covariance structures, and can estimate the power of various trial designs. The value of genetic, biochemical, and neuroimaging biomarkers for subject selection, reduction of explained variance, and supportive outcome measures can likewise be explored.

There is a growing consensus that the optimal population for disease-modification programs is not AD dementia, but rather pre-dementia individuals on the spectrum of AD neurobiology [7]. It is reasonable to assume that interventions targeting the pathophysiologic mechanisms underlying AD will have the greatest effect before the pathology is at the advanced stage that corresponds to dementia. Many efforts are under way by academic, industry, foundation, and government groups to facilitate this direction; these efforts include proposed revisions to diagnostic criteria, and various meetings and task forces to explore trial design issues.

ADNI data have provided the basis for much of this work. ADNI has focused on amnestic MCI, and has included the leading candidate outcome measures and biomarkers, allowing assessment of proposed trial designs. Importantly, ADNI data have revealed that appropriate use of standard outcome measures and biomarkers can yield powerful and feasible trial designs for the pre-dementia (MCI) population.

Table 3
Clinical trial design scenarios utilizing change in continuous outcomes being explored in ADNI [Reproduced from Alzheimer's Res Ther, 2009;1:2 with permission.]

	Mild AD Trial	Early AD Trial	Very Early AD Trial
Cognitive Status	Mild dementia	Mild cognitive impairment	Cognitively normal
Clinical Dementia Rating global score	0.5–1	0.5	0
MMSE range	16–26	25–30	28–30
Biomarker for subject selection	None	Amyloid imaging and/or CSF $A\beta_{42}$	Amyloid imaging and/or CSF $A\beta_{42}$
Biomarker for subject stratification	None or *APOE* genotype	*APOE* genotype	*APOE* genotype
Primary cognitive outcome measure	ADAScog11	ADAScog12 (includes delayed recall)	Sensitive memory and/or executive function test
Primary global/functional outcome measure	CDR-SB	CDR-SB	None
Analysis covariates	Baseline cognition and regional brain volume	Baseline cognition and regional brain volume	Regional brain volume
Biomarker outcome	Regional brain atrophy	Regional brain atrophy	Regional brain atrophy (as surrogate endpoint)
Duration of treatment	18 mo	24 mo	24–36 mo
Primary analysis	Change score or slope of cp-primaries: ADAScog11, CDR SB	Change score or slope of co-primaries: ADAScog12, CDR-SB	Regional brain atrophy rate and cognitive decline

Specifically, ADNI 1 data [8] indicate the following:

a. The CDR-SB is a powerful outcome measure in mild AD and MCI.
b. In MCI, the ADAS-cog13 (which includes delayed word recall and number cancellation tasks) is superior to the ADAS-cog11 in a 24-month trial.
c. Covariates reduce samples sizes by 10%–15% in LMCI and mild AD.
d. Selection of LMCI subjects using CSF $A\beta_{42}$ reduces sample sizes.

Rate of change designs in comparison with survival to dementia designs, and the effect of biomarker selection and covariates.

We have used ADNI data to propose study designs (Table 3) for disease-modifying interventions in the pre-dementia population [8]. For such a trial, it is rational to select subjects with evidence of amyloid accumulation in brain; ADNI data suggest that amyloid PET imaging and low CSF $A\beta_{42}$ are equivalent indicators of amyloid accumulation. Subjects meeting the ADNI criteria for amnestic MCI and selected based on an abnormal amyloid biomarker would meet the proposed research criteria for AD [9], and consensus meetings suggest that standard AD-type cognitive and clinical co-primary outcome measures will be appropriate for pivotal trials, and a single clinical measure may be appropriate for a phase II proof of concept trial. Using ADNI data, we have shown that a 2-year treatment period in this population, with appropriate covariates, has reasonable power to demonstrate effects on primary measures (Donohue et al., unpublished observation). A design similar to this has recently been launched as a phase II proof of concept trial of a secretase inhibitor (ClinicalTrials.gov identifier NCT00890890).

Table 4
Comparison of imaging and cognitive/clinical outcome measures to power trials

	Hippocampal volumes (average, L and R, Dale)*	FDG-PET (Jagust)†	ADAS-cog 11	MMSE	CDR-SB
MCI	208	3360	4099	4162	954
AD	99	255	407	632	465

* Average of left and right hippocampal volumes, as calculated by Anders Dale's laboratory at the University of California San Diego.

† Posterior cingulated activity on FDG-PET scanning, as calculated by William Jagust's laboratory at UC Berkeley.

5. The potential value of neuroimaging measures as surrogate outcomes

ADNI data have confirmed that the annual change and variance for neuroimaging measures provide much better power to detect disease-slowing effects than do standard cognitive and clinical measures.

Table 4, for example, provides group sizes for a study aiming to demonstrate a 25% slowing of disease progression as indicated by 1 year change in various outcome measures (analyzed by linear mixed effects models), with 80% power and an alpha of .05. In general, we observe that hippocampal volumetric change has excellent power in AD and MCI. This suggests that for an intervention expected to slow clinical progression and brain atrophy, a phase II 1 year proof of concept trial in AD might be conducted with reasonable group sizes. The sample sizes in Table 4 can be substantially reduced by the incorporation of biomarker selection criteria and covariates.

To extend this idea further, we have found that 6 month change in volumetric MRI measures provide good power to

demonstrate slowing of progression in MCI. For example, a 6-month trial to demonstrate 25% slowing in AD and MCI would require 1055 and 13,074 subjects using the ADAS-cog, 1084 and 3388 using the CDR-SB, but only 216 and 528 for hippocampal volume. If we optimize biomarker selection and covariates, a 6-month proof of concept study is feasible. We note that the 6 month change in hippocampal volume is highly correlated with later interval changes, and is correlated to later decline in cognitive and clinical measures.

6. ADNI GO and EMCI

The continuation of ADNI has been greatly facilitated by the award of funds through the NIH Grand Opportunity program. It provides support to ADNI activities over a 2-year period, overlapping with and supplementing the first year of this proposed ADNI 2 project. Specifically, the GO award is supporting the following Clinical Core activities:

1. Two years of longitudinal follow-up for the original ADNI, late MCI (LMCI), and cognitively normal (CN) cohorts.
2. The recruitment of a new cohort of EMCI subjects with milder episodic memory impairment than classical LMCI subjects enrolled in ADNI 1.
3. The addition of new cognitive and clinical measures.
4. Additional biomarker and imaging data collection (as described in the corresponding sections of this application).

The EMCI group is a newly characterized set of subjects to be recruited in the GO grant funding period. To assess the clinical characteristics of the EMCI and LMCI subject groups, we interrogated the database from the NIA-sponsored Alzheimer's Disease Center Program through the National Alzheimer's Coordinating Center (NACC) under the direction of Dr Walter Kukull. We used the NACC database because it represents subjects who were classified as MCI, using essentially the same criteria proposed in ADNI. However, because there was no sub-categorization of EMCI or LMCI in the NACC database, we imposed the proposed criteria and instruments for ADNI GO and ADNI 2 on previously collected aMCI subjects. The summary of the cognitive characteristics of LMCI subjects from ADNI 1 has been described earlier, but the features of EMCI subjects have not been characterized, and consequently, a comparison of these two clinical groups at baseline and with respect to rates of progression from the NACC database is shown in Table 5. The EMCI subjects represent individuals with milder degrees of cognitive and functional impairment than the LMCI subjects, and their rate of progression is slower. We anticipate the subjects recruited in ADNI 2, summarized in Table 6 and enumerated in Table 7, will conform to these general clinical characteristics.

Table 5
MCI data from NACC; annual rates of progression and instrument means

	EMCI (N = 181)	LMCI (N = 369)
Progression to dementia (Year 1)	12%	27%
Progression to CDR 1 (Year 1)	7%	15%
MMSE		
Baseline	28.0 (1.6)	27.3 (1.8)
Year 1	27.6 (2.1)	26.2 (2.8)
CDR–SB		
Baseline	1.2 (0.9)	1.5 (1.0)
Year 1	1.6 (1.3)	2.1 (1.6)
FAQ		
Baseline	3.7 (5.3)	4.7 (5.6)
Year 1	5.5 (6.9)	6.5 (6.4)

Table 6
Characteristics of four ADNI cohorts and Logical Memory delayed recall cutoff scores (see text)

	CN	EMCI	LMCI	AD
CDR	0	0.5	0.5	0.5–1
MMSE	24–30	24–30	24–30	20–26
LM-DR (cutoffs)				
Education				
0–7	≥3	3–6	≤2	≤2
8–15	≥5	5–9	≤4	≤4
≥16	≥9	9–11	≤8	≤8
Dementia	No	No	No	Yes

7. Primary care physician instruments

Because MCI is a sufficiently mild condition, it is most likely that individuals with this degree of cognitive complaint will present initially to primary care physicians (PCP). As such, there is a need to develop instruments that can be administered efficiently and inexpensively in the PCP setting to allow the clinicians to determine which patients might be candidates for further evaluation, and possibly therapies. Toward this end, we have selected a brief cognitive instrument to allow detection of the cognitive aspects of MCI and a functional instrument to determine the degree of functional impairment.

The primary screening tools for ADNI to determine whether a person is eligible for the trial involve delayed recall of one paragraph from the Logical Memory subtest of the Wechsler Memory Scale-Revised to provide a metric of memory function to corroborate the individual's cognitive complaint, and the CDR to be certain that the degree of memory function represents a change from the previous level of performance. The combination of these instruments is designed to determine that a person is cognitively and functionally

Table 7
Number of subjects followed in ADNI 2, including those recruited in ADNI 1 and ADNI GO

	ADNI 1	ADNI GO	ADNI 2	Cumulative
CN	202		150	352
EMCI		200	100	350
LMCI	274		150	424
AD			150	150

impaired but not to the extent that they would constitute criteria for dementia. However, using the Logical Memory paragraph and the CDR would be too time consuming in the PCP setting, and consequently, brief instruments need to be evaluated to see whether they may be appropriate for the PCP.

The brief cognitive instrument that has been selected is the Montreal Cognitive Assessment test (MoCA) that is designed to detect subjects at the MCI stage of cognitive dysfunction [9]. This instrument has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The MoCA is believed to be more sensitive than general screening instruments, such as the Mini-Mental State Examination (MMSE) or the Short Test of Mental Status. The MoCA can be administered in approximately 10 minutes.

For a functional assessment, we have selected the Measurement of Everyday Cognition (ECog) [10]. This instrument has been developed to assess functional impairment of a very mild nature, as can be seen in MCI. The ECog is an informant-rated questionnaire that comprises multiple subscales and takes approximately 10 minutes to administer. Previous research on this instrument indicates that ECog correlates well with established measures of functional status and global cognition but only weakly with age and education. ECog was able to differentiate among cognitively normal, MCI, and AD subjects. Results of ECog suggest that it is a useful tool for the measurement of general and domain-specific everyday functions in the elderly.

The MoCA and ECog will be administered to all participants in ADNI GO but will not be used for any screening or diagnostic decisions themselves. Rather, the traditional screening measures involving the single paragraph from the Logical Memory subtest and the CDR will be used to determine the appropriate level of function for subjects in ADNI GO just as it was in ADNI 1. However, the performances of the MoCA and ECog will be followed up to determine their ability to differentiate among the four groups.

8. Plans for ADNI 2

ADNI 2, if funded, will continue and build on the aims of ADNI 1 and ADNI GO. All cognitively normal (CN), EMCI, and LMCI subjects will be followed up into the new grant period, providing up to 10 years of longitudinal data on these normal and mildly impaired subjects. This will be essential to inform the model proposed in Fig. 1, and link early cognitive, clinical, and biomarker changes to later clinically important decline. Cross-sectional and longitudinal characterization will continue, including documentation of conversions across diagnostic categories. In particular, the long-term characterization of CN and EMCI subjects, including LPs, amyloid imaging, FDG-PET, and volumetric MRI, will facilitate trial design in these critically important populations. Important subgroups within these cohorts will be defined by amyloid biomarkers and *APOE* genotype.

In ADNI 2, we will extend this still further, by adding 3-month volumetric MRI scans for all newly enrolled subjects, to explore the feasibility of this measure for brief proof of concept trials, and for interim analysis/adaptive designs for longer trials.

The goal of ADNI 2 is to obtain as close to 100% participation in lumbar puncture as is feasible. ADNI 1 aimed for 25% participation and achieved more than 50% participation. For ADNI GO and ADNI 2, we aim to limit recruitment to those that consent to LP. Exceptions will be made to meet other goals such as minority recruitment.

9. ADNI 2 clinical trial design aims: Extending the results from ADNI 1

As described earlier, ADNI 1 data suggest the feasibility of longitudinal change designs in selected LMCI subjects selected for amyloid accumulation using CSF $A\beta_{42}$. In ADNI 2, we will enroll 150 additional LMCI subjects, and all (or nearly all) will have both CSF $A\beta_{42}$ and ^{18}F AV-45 amyloid imaging. We will, thus, have an independent sample of size similar to that used for the ADNI 1 power estimates. We will confirm the utility of CSF $A\beta_{42}$ selection, the equivalent value of AV-45 amyloid imaging, the utility of genotype and MRI volumetric (and other disease stage) covariates, and confirm the group size estimates.

We hypothesize that it will be feasible to extend these ideas to the milder EMCI population. That is, we propose that selection of EMCI subjects by amyloid markers, and using disease stage and *APOE* covariates, with CDR-SB alone or with ADAS-cog as continuous outcomes, we will have reasonable power to demonstrate disease modifying effects. We expect that clinical effects of modifying disease mechanisms will be greater at the earlier EMCI stage, offsetting the slower rates of decline. Thus, we may have similar group sizes to power EMCI studies to demonstrate a 40% effect as we do to power LMCI studies to see a 30% effect.

We also hypothesize that longitudinal change designs will be advantageous compared with survival to AD in the EMCI population, as it is in LMCI.

10. ADNI 2: Extending clinical trial design evaluation to the EMCI population

The evaluation of the EMCI cohort will include analysis of longitudinal trajectories of cognitive and clinical assessments, MRI volumetric measures, FDG-PET, as well as amyloid imaging and CSF markers. The effect of *APOE* genotype (and potentially other genetic markers) on these trajectories will be assessed. Subgroups selected by amyloid biomarkers, as well as cutoff values of hippocampal volume, FDG-PET activity, and cognitive and clinical assessments will likewise be examined. The value of biomarker covariates in reducing unexplained variance of longitudinal change will be analyzed.

A major purpose of examining this new cohort in this manner will be to inform trial design. We hypothesize that we will be able to extend similar design features that have

yielded exciting findings in the LMCI cohort to this more mildly impaired population. We aim to provide feasible trial designs for studies enrolling EMCI subjects.

Our specific hypothesis is that we can select subjects using amyloid biomarkers (AV-45 imaging or CSF $A\beta_{42}$), perhaps also using *APOE* genotype selection, to define an EMCI subpopulation with longitudinal decline on standard or supplemented measures that will allow proof of concept and pivotal testing of disease-modifying agents. Although amyloid biomarkers represent primary selection candidates, we will also evaluate other biomarkers including CSF tau and P-tau (noting that the latter may be particularly appropriate for neuroprotection and kinase inhibitor studies, respectively).

11. ADNI 2: Extending trial designs to the asymptomatic population

As indicated in Table 2, we expect that cognitive and clinical measures will not be feasible outcomes in symptomatic individuals, even those selected using biomarkers. Although we expect to see some decline in standard measures, at this stage the efficiency of such measures is unlikely to yield feasible trial sizes. In this population, we hypothesize, however, that potential surrogate measure will allow proof of concept trial design. That is, as we increase our recruitment and long-term follow-up of asymptomatic subjects during ADNI 2, we will explore the trajectories on imaging measures (such as entorhinal cortex atrophy, regional cortical thickness measures, and FDG-PET measures) in subjects selected on the basis of genotype and/or markers of amyloid or tau pathology.

An essential aim of ADNI 2 is also to examine the relationship between longitudinal change and later conversion to dementia in asymptomatic, EMCI, and LMCI subjects. In addition to the comparison of longitudinal change and survival to diagnosis trial designs, this will strengthen the link between (ie, establish the predictive value of) early change in cognitive, clinical, and biomarker measures to later clinical progression. Although the experience of interventional studies will be essential, the ADNI 2 analyses can support the validation of potential surrogates by establishing predictive value.

12. Summary

The ADNI experience has been enlightening in demonstrating that clinical, imaging, and chemical biomarker data can be reliably collected in a multicenter study. The standardization of procedures has been accomplished, and well-characterized cohorts of clinical subjects have been recruited and followed up. The continued participation rate has been excellent, and the longitudinal data have informed numerous studies on AD neurobiology and have provided important guidance to clinical trial design. The true value of these data reside in the long-term follow-up of the subjects to carefully map the cognitive, clinical, biochemical, and neuroimaging changes across the full spectrum of Alzheimer's pathology, guiding the development of effective interventions.

Acknowledgments

This work was supported by grants (U01-AG024904, U01-AG10483) from the National Institute on Aging of the National Institutes of Health.

References

[1] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010;74:201–9.

[2] Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143–53.

[3] Jack CR, Knopman D, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

[4] Petersen RC. Alzheimer's disease: progress in prediction. Lancet 2010; 9:4–5.

[5] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR Jr. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447–55.

[6] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.

[7] Rafii MS, Aisen PS. Recent developments in Alzheimer's disease therapeutics. BMC Med 2009;7:7.

[8] Aisen PS. Alzheimer's disease therapeutic research: the path forward. Alzheimers Res Ther 2009;1:2.

[9] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.

[10] Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, Decarli C. The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology 2008; 22:531–44.