Published in final edited form as:
Int Rev Psychiatry. 2008 August ; 20(4): 389–395. doi:10.1080/09540260802094548.

Controversies in Alzheimer's disease drug development

Jeffrey L. Cummings
Departments of Neurology and Psychiatry, and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract

Understanding of the pathophysiological basis of Alzheimer's disease (AD) is increasing rapidly and a variety of potential treatment modalities have emerged based on these improved mechanistic insights. The optimal way of proceeding with disease-modifying drug development remains to be clarified and controversies have emerged regarding the definition of Alzheimer's disease, the participation of mild cognitive impairment patients in clinical trials, the definition of disease modification, the potential impediments to satisfaction from patients receiving disease-modifying therapy, the importance of add-on therapy with symptomatic agents, the optimal clinical trial design to demonstrate disease modification, the best means of minimizing time spent in Phase II of drug development, the potential role of adaptive designs in clinical trials, the use of enrichment designs in clinical trials, the role of biomarkers in clinical trials, the treatment of advanced patients with disease-modifying agents, and distinctions between disease modification and disease prevention. The questions surrounding these issues must be resolved as disease-modifying therapies for AD are advanced. These controversies are framed and potential directions towards resolution described.

Introduction

There has been rapid progress in understanding the molecular neurobiological basis of Alzheimer's disease (AD). Studies of disease mechanisms have identified a number of potentially exploitable critical steps that may represent opportunities for treatment. Intervention at the level of amyloid beta (Aβ) processing, tau hyper-phosphorylation, excitotoxicity, inflammation, or apoptosis would result in preservation of nerve cells with a concomitant impact on disease onset or disease progression. The promised emergence of such disease-modifying treatment raises many questions about how to proceed both with clinical trial design and implementation of disease modifying interventions. Major controversies involved in development of disease modifying therapies and application to AD patients are considered here.

Definition of Alzheimer's disease

For purposes of research diagnosis and clinical trial enrollment the most commonly used diagnostic criteria have been those of the National Institute of Neurological and

Correspondence: Jeffrey L. Cummings, MD, UCLA Alzheimer Disease Center, 10911 Weyburn Avenue, Suite 200, Los Angeles, CA 90095, USA. Tel: +310 794 3665. Fax: +310 794 3148. jcummings@mednet.ucla.edu.

Disclosures

Dr Cummings has provided consultation to the following pharmaceutical companies: Astellas, Avanir, Eisai, EnVivo, Forest, Janssen, Lilly, Lundbeck, Merck, Novartis, Ono Pharma, Pfizer, Sanofi-Aventis, and Takeda.

Declaration of interest: The author discloses conflicts of interest as noted above. The author alone is responsible for the content and writing of the paper.

Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)(McKhann et al., 1984). Most trials have enrolled patients meeting criteria for probable AD, requiring deficits in memory and one other cognitive domain, established by clinical examination and documented by neuropsychological testing in patients who have no disturbance of consciousness and no alternative cause for their cognitive abnormalities.

In the past decade there has been more attention to a prodromal state that precedes the dementia of AD called mild cognitive impairment (MCI) (Petersen et al., 2001). The most commonly used criteria for MCI require that the patient (or caregiver) have a complaint regarding the patient's memory, there are abnormalities of memory or other cognitive domains the patient does not have impairment of activities of daily living, and the patient does not meet criteria for a dementia syndrome. MCI is a non-specific syndrome which may evolve into AD, or into another dementia, may remain stable, or in rare cases may recover to normal cognition. There is increasing evidence that the amnestic form of MCI is usually prodromal to dementia of the Alzheimer type, and represents the earliest manifestation in AD.

It is artificial to divide the course of a disease into mild and more severe forms as if they represented different clinical entities. Alzheimer's disease is an insidiously progressive illness that advances from normal cognition to mild degrees of cognitive impairment not meeting criteria for dementia to more severe cognitive impairment meeting criteria for dementia of the Alzheimer type. Dubois and colleagues (2007) have proposed criteria that may help resolve the MCI controversy. They suggest that AD can be diagnosed in patients who have an episodic type of memory abnormality (typical of AD) and have biomarker evidence consistent with the presence of AD. Potential biomarkers include medial temporal atrophy on structural brain imaging, abnormal cerebrospinal fluid (CSF) consistent with the diagnosis of AD (high levels of phospho-tau and low levels of Aβ peptide), positron emission tomography (PET) showing diminished glucose metabolism bilaterally, or abnormal amyloid signal on Pittsburgh Compound B (PIB) or other amyloid imaging, or a proven AD autosomal dominant mutation within the immediate family. Most MCI patients who progress to AD show biological marker evidence of the presence of the Alzheimer process in the brain. Thus, the combination of the classical type of memory abnormality characteristic of AD and the presence of a biomarker indicative of the Alzheimer process would allow seamless identification of patients with AD meeting current criteria of either MCI or dementia of the Alzheimer type.

The criteria might not include all patients with AD, especially those with atypical presentations. However, they are predicted to have few false positives and will assist in recruiting a more homogeneous population of patients who have AD into clinical trials. Research investigation of these criteria to determine their sensitivity, specificity, and positive and negative predictive value are needed.

Definition of disease modification

There is no consensus definition of disease modification but there has been an evolution towards this goal. Mani (2004) suggested that disease modification requires that the intervention address the underlying neurobiological processes leading to cell death. Cummings (2007) recommended that a two-fold definition of disease modification is required: (1) intervention in the underlying process of cell death and (2) impact on a clinically relevant milestone. Sampaio (2006) suggested that delay of a clinically meaningful milestone is sufficient to label a compound as disease modifying. Many investigators would choose to label the latter as disease course modifying, saving the appellation of 'disease

modifying' for those compounds with a known mechanism of action impacting the underlying process of AD. Symptomatic agents may impact disease course, delaying important clinical milestones, without necessarily addressing the underlying pathological processes for the diseases (Mohs, Kawas, & Carrillo, 2006).

Unresolved issues remain regarding the definition of 'clinically relevant' milestones and on how best to establish that a compound has an impact on the underlying disease process.

Drug labelling by regulatory authorities

Related to the uncertainties regarding the definition of disease modification is the question of how regulatory authorities will consider drug labelling for this class of agents. Most evidence of the impact on underlying processes of a therapeutic compound is inferential in nature. For example, magnetic resonance imaging (MRI) evidence of medial temporal atrophy (MTA) suggests that an underlying disease process has been affected, but provides no insight into the mechanism of action of either the disease or the drug. A combination of clinical trial evidence of delay in progression and MRI evidence of reduced MTA might suffice for labelling such as 'delaying disability', 'slowing progression', or reducing the rate of brain atrophy. More mechanistic evidence is likely to be required for stronger labelling.

Cerebrospinal fluid markers provide more insight into the effect of agents on AD-related processes. Inhibitors or modulators of gamma-secretase might lead to a reduction in Aβ CSF as Aβ production is inhibited. If Aβ precedes tau hyper-phosphorylation and oxidation in a disease cascade, then phosphorylated-tau and isoprostanes (a measure of oxidative damage) might be expected to fall following successful intervention with an anti-Aβ therapy. Such observations would support variants of disease-modifying labelling, especially if correlated with clinical changes. They would not serve as surrogate measures substituting for clinical measures unless proven to predict clinical response.

There is an opportunity in the clinical pharmacology section of the prescribing information (package insert) to describe what is known of the mechanism of action of the therapeutic agent. The combination of the clinical pharmacology description, clinical trial evidence of delayed progression, and biomarker evidence of impact on underlying disease may be sufficient to persuade the prescribing community that the agent has properties in excess of symptomatic relief.

Clinical trial designs to demonstrate disease modification

Clinical trials for symptomatic compounds have generally been short term (typically 6 months in duration) and seek a drug-placebo difference at endpoint. This is the design used for trials of currently approved cholinesterase inhibitors and memantine. A symptomatic benefit is demonstrated by continuing decline in the placebo group and improvement or delay of progression in the active treatment arm of the study. Disease modifying clinical trial designs seek to provide evidence that the course of the disease is being affected by the therapeutic intervention. Two trial designs have been proposed to provide evidence of this type: (1) the staggered start design, and (2) the staggered withdrawal design (Cummings, 2007). In the staggered start design patients are randomized to an active intervention arm or a placebo arm, and patients on placebo are given active therapy after a delay. If the delayed treatment arm 'catches up' in therapeutic response with the initial therapy arm, the drug response is symptomatic; on the other hand, if the delayed treatment arm fails to improve to the degree demonstrated by the active treatment arm then disease modification is supported. In the delayed or randomized withdrawal design all patients are treated with the active agent, and after a specific period of time one group is randomly withdrawn from therapy. If those withdrawn descend to the projected level of function of an untreated group, or of a placebo

group, then the treatment response has been symptomatic. If however, the group withdrawn does not descend to the level of an untreated group, then disease modification can be inferred. There are many challenges and controversies associated with these designs and they have not been implemented in clinical trials leading to drug approval of anti-dementia agents by regulatory authorities. In the staggered start design it is uncertain how long patients might require treatment before a therapeutic response could be demonstrated. In addition, the two arms of the trial are starting at different levels of disease severity, and it is not clear how this might affect the calculation of therapeutic response. Attrition would also affect confidence in this trial design. The delayed or staggered withdrawal design faces similar issues. It is unknown how long patients should be treated or withdrawn to demonstrate therapeutic efficacy. In addition, there may be ethical challenges to withdrawing a patient group from therapy. An alternative approach called the 'natural history staggered start design' has been proposed as a means of deriving staggered start type of information from a parallel group design through statistical analytic approaches (Hendrix et al., 2007).

An alternative to the staggered start and staggered withdrawal designs is a two-arm design in which the slope of progression of the placebo arm is compared with slope of progression in the active treatment arm. If disease slowing is achieved, the slope of the active treatment arm will be reduced compared to the slope of the placebo arm. Over the course of time, there should be an increasing divergence of outcomes between the active treatment group compared to the placebo group. In addition to the slope analysis, this design affords a direct endpoint comparison similar to that used in trials of symptomatic agents. The regulatory view of slope analysis has not been established.

Another clinical trial design potentially useful in clinical trials of disease modifying agents is the delay to milestone approach. Two examples of such designs have been executed by the Alzheimer Disease Cooperative Study (ADCS). In a trial comparing vitamin E, selegiline, the combination of these two agents, and placebo, patients entered the trial when they met Clinical Dementia Rating (CDR) scale scores of 2 and exited the trial when they had progressed to CDR scores of 3. Thus delay of a CDR score of 3 represented a delay to milestone in this trial (Sano et al., 1997). Similarly, in a trial comparing the efficacy of donepezil, vitamin E, and placebo in patients with MCI, the principal outcome was progression to AD (Petersen et al., 2005). A consensus method was used to establish progression from MCI to AD. The principal objection to progression to clinical milestone-type designs is that most clinical milestones are relatively arbitrary and do not present changes in underlying pathophysiology or neurobiology.

The optimal clinical trial design to demonstrate disease modification is uncertain. A parallel group design utilizing endpoint difference or a delay to milestone design may have the most to recommend them. Further support for disease modification by including biomarkers in the trial would be required for disease modification-related labelling.

The phase II conundrum

There is a marked unmet need for effective therapy for AD and MCI. Patients are in urgent need of disease modifying and symptomatic therapies. Pharmaceutical and biotechnology companies also desire rapid market entry to optimize their investment in drug development and to minimize disadvantages with regard to competitors. The traditional clinical development plan includes phase I first-in-human studies with single ascending doses followed by multiple ascending doses to establish safety in human populations. In the classical paradigm phase I is followed by a phase IIa proof of concept (POC) study providing preliminary evidence of efficacy and phase IIb dose-finding studies establishing

the optimal dose or doses across the range of dose alternatives. Phase II data are used to design phase III clinical trials that will be presented to regulatory authorities at the time of new drug application (NDA) for marketing approval. The entire process may take 12 to 15 years, leaving only a few residual years of the 20-year patent protection afforded to new drugs (Rang, 2006).

Development of disease modifying drugs represents a particular challenge to the usual temporal sequence of drug development. Demonstration of disease modification using clinical outcomes and achievable sample sizes will require 12 to 18 months. Thus, several years of patent life will be expended in phase II to establish POC and optimal dosing. 'The phase II conundrum' revolves around the question of how little date can be used to form an adequate platform in phase II for launching a phase III trial. Phase III trials are the most expensive phase of drug development, and proceeding to phase III with inadequate phase II data increases the likelihood of failure at great expense to the industry sponsor. Abandoning a drug after a negative phase III trial, when there has been inadequate dose finding in phase II, may also result in overlooking potentially beneficial drugs not tested at optimal dosage strengths. Potential contributing solutions for the phase II conundrum include legislative relief to extend patent protection for disease modifying compounds, development of biomarkers that are more responsive and can serve in place of clinical measures or at least assist in drug development decisions, development of more sensitive clinical measures that will reflect drug activity in smaller populations or in shorter trials, or the use of clinical trial designs that may shorten phase II (such as the adaptive designs discussed below).

Adaptive clinical trial designs

Adaptive clinical trial designs allow alterations in dose, population, or endpoint after the initiation of the trial. The most commonly used adaptive approach uses ongoing information to optimize dosage choices in the course of the trial. Those arms with no clinical response suggesting the futility of further study or not meeting criteria for a minimally effective clinical improvement are abandoned and enrollees randomized to more promising treatment arms. Decisions are made on the basis of interim analysis (Wang, Hung, Tsong, & Cui, 2001). Using adaptive designs, phase II may proceed seamlessly and without interruption into phase III with continuation only of the potentially useful dose arms and placebo. This integration of phase II and phase III eliminates the end of phase II analysis and delayed initiation of phase III, saving up to 18 months of study time and patent life. Adaptive designs must be completely pre-specified in order to avoid erosion of trial credibility. Regulatory authorities have limited experience with adaptive designs and must be included in discussions development in order to base important trial decisions on such approaches (Chang, Chow, & Pong, 2006).

Other design changes that can possibly be implemented with adaptive strategies include altering patient selection. For example, if interim analysis demonstrates that therapeutic response is limited to a specific patient group (e.g., mild degree of cognitive impairment, patients carrying the apolipoprotein e-4 allele) then recruitment criteria can be altered to favour or enrole exclusively responsive patient populations. Again, pre-specification is of paramount importance to maintain trial credibility.

Enrichment designs

To obtain POC, trials could consider using an enrichment strategy of enrolling patients who are progressing more rapidly and allowing demonstration of a drug placebo difference in a shorter period of time. Patients with MCI or early AD likely to progress to a dementia of the Alzheimer type or more severe disease can be identified by epidemiologic, clinical, and biomarker means (Cummings, Doody, & Clark, 2007). Epidemiologic risk factors include

more advanced age, female sex, history of head trauma, history of mid-life hypertension, history of stroke, and small head circumference (Cummings et al., 2007). Genetic predictors of more rapid progression include Apoe 4 genotype, SORL1 genotype, and family history of AD. Physiological predictors of more rapid progression include hypothyroidism, hypercholesterolemia, diabetes, low diastolic blood pressure, and elevated serum homocysteine levels (Cummings et al., 2007). Medial temporal atrophy on MRI, parietal hypometabolism on Fluxodexoglucose (FDG) PET, or the presence of intracerebral amyloid on PIB or FDDNP scans likewise predict the presence of the AD process in patients with MCI. A combination of risk factors could be used to establish a population of patients likely to progress to more severe disease in shorter periods of time, facilitating identification of a drug placebo difference for efficacious compounds. Recruitment of patients age 80 or older, those with an e4 allele or those with a defined level of intracerebral amyloid, might provide the basis for POC studies. A current contradiction in execution of clinical trials is that individuals participating in trials tend to be younger, healthier, and have fewer risk factors for progression, thus minimizing progression.

Clinical trial instrumentation

Variability in clinical measures increases the sample size necessary to demonstrate a drug-placebo difference. Biomarkers typically have smaller standard deviations and therefore smaller samples are required when they are used as clinical trial outcomes (Jack & Petersen, 2000). The large standard deviations apparent on clinical instrumentation may reflect intrinsic human variability in cognition secondary to differences in alertness, arousal, engagement, distraction, and emotional state. Alternatively, large standard deviations in clinical measures may in part be attributable to shortcomings of the commonly used instruments. The principle cognitive outcome in current clinical trials for AD and MCI is the Alzheimer's Disease Assessment Scale Cognitive portion (ADAS-Cog) (Rosen, Mohs, & Davis, 1984). This is a 70-point scale with higher scores indicating greater impairment. It measures language, praxis, and memory. The ADAS-Cog is typically insensitive to cognitive changes occurring in patients with mild AD, shows its most rapid change over time in patients with moderate AD, and is again relatively insensitive to changes in patients with severe disease. An alternative instrument increasingly utilized in clinical trials is the Neuropsychological Test Battery (NTB) (Harrison et al., 2007). This instrument includes memory and executive factors. Memory is critical to the presence of AD and executive dysfunction is common in MCI and AD. There are no executive measures of the ADAS-Cog. The NTB appears to be equally sensitive to change in patients with mild AD and those with moderate AD, suggesting that it may be a superior instrument in patients with limited cognitive abnormalities. Given the long experience with the ADAS-Cog in clinical trials it will be important to understand the correspondence between these two instruments as clinical trial methods advance. Alternative instrumentation also can be considered.

Computerized assessments have some advantages over standard paper and pencil neuropsychological assessments (Doniger et al., 2006). They can measure reaction time and speed of cognitive processing, unavailable on most non-computerized test batteries. The standardized administration may also minimize site-to-site variability and further reduce the standard deviations observed in clinical trials. However, changes as measured by computerized assessment must be translated into conventional cognitive and functional benefit to assist with drug development. A strong correspondence between computerized outcomes and standard clinical outcomes might allow the substitution of computerized measures for standard clinical measures in POC or dose-finding trials. This would facilitate advancing compounds more rapidly through phase II. Substantially greater experience with specific computerized measures or batteries will be required before confidence in such surrogacy is achieved.

The clinical meaningfulness of cognitive changes is often established by concurrent benefit of activities of daily living. Activities of daily living scales tend to be less sensitive than cognitive scales to drug-related changes and improvements in sensitivity of cognitive measures will require a concomitant improvement in the sensitivity of activities of daily living measures.

The role of biomarkers in drug development

Biomarkers can play several roles in drug development: (1) identifying patients for inclusions in clinical trials, (2) providing insight into pharmacologic engagement of the target, (3) monitoring the success of therapeutic intervention, and (4) substituting for clinical measures.

Dubois and colleagues (2007), as noted above, have proposed that a combination of episodic memory defect and biomarker is sufficient to establish a diagnosis of AD. This is an example of the use of a biomarker to establish a diagnosis and to provide criteria for enrollment in a clinical trial. Alternative examples of establishing a diagnosis with biomarkers would be enrolling patients with CSF hallmarks of AD (elevated phospho-tau and reduced Aβ peptide) or evidence of intracerebral amyloid on PIB or FDDNP scans. Bilateral parietal lobe metabolism on FDG PET or MTA on MRI also provide presumptive evidence of the presence of AD and could be used as entry criteria for a clinical trial.

Some biomarkers might provide evidence into a pharmacologic engagement with the therapeutic target. For example, beta-secretase can be measured in cerebrospinal fluid (Verheijen et al., 2006) and reduction of beta-secretase activity after administration of a beta-secretase inhibitor would be evidence of target engagement. More specific biomarkers will emerge as new compounds and their therapeutic targets are developed.

Some biomarkers might provide evidence of the success of therapeutic intervention. For example, reduction in amyloid levels as measured by PIB or FDDNP would be evidence of reduced levels of insoluble amyloid in the brain. Such a marker may be important in Aβ related interventions. Similarly a reduction in the rate of MTA as measured by MRI would provide evidence of disease modification.

No biomarker has been sufficiently well validated to function as a surrogate marker. Development of surrogate markers is an important goal since substitution of surrogate markers for clinical measures would allow the use of smaller patient populations in clinical trials or shorter periods of drug exposure to establish a drug-placebo difference. A surrogate marker must be shown to predict the clinical response, correlate with the clinical response, and be related to the mechanism of drug action (Katz, 2004). Inclusion in clinical trials of currently available biomarkers is the first step towards eventual development of a validated surrogate marker.

Patient perception of disease modification

Patients with symptoms want symptom relief and to function at a normal level. Current disease modifying compounds are expected to slow progression, but most are not expected to improve current symptoms. Successful development of a disease modifying compound may leave patients unsatisfied as they progress more slowly but nevertheless inevitably. The development of disease modifying compounds that also provide symptomatic improvement or co-administration of disease modifying and symptomatic treatments will be necessary to meet the needs of symptomatic patients.

Symptomatic anti-Alzheimer therapies

Current symptomatic therapies (cholinesterase and maemantine) are valuable, delaying decline in a majority of patients and providing improvement in a minority. The degree of improvement is modest and in most cases is within the standard error of measurement of instrumentation used to assess the change. Neither patients nor physicians are routinely able to detect the relatively subtle changes induced by these treatments. Development of more effective symptomatic therapies that produce a greater magnitude of response, have a more rapid onset of action, have a more persistent duration of action, and are well tolerated is an important goal of drug development for AD. Symptomatic agents will be routinely used in combination with disease modifying therapies.

Treatment of patients with advanced Alzheimer's disease

An ethical and moral challenge awaits the development of disease modifying therapies. There will be no uncertainty about the importance of intervening in patients with MCI or patients with early AD. Prolongation of the later phases of AD, however, is likely to be met with uncertainty. Some families will desire prolongation of survival regardless of the state of function of the patient. Others may see nearly any degree of compromise as eroding the individual's quality of life and would object to disease modifying interventions. Disease-modifying agents may be expensive or may have important side effects which will require consideration as they are integrated into healthcare plans. Patient advocacy groups, pharmaceutical and biotechnology companies, patients and caregivers, and clinicians must all engage in the dialogue around the appropriate implementation of disease modifying therapies.

Disease modification or disease prevention?

It is commonly posited that the Alzheimer process is present in the brain for several to many years prior to the onset of symptoms. Experience with PIB in normal elderly suggests that amyloid is accumulating in some cognitively normal people who presumably will progress through the stages of MCI and dementia of the Alzheimer type. The relative stability of the amyloid signal on PIB imaging from MCI through more advanced AD suggests that maximal amyloid deposition may occur early in the disease process and the disease progression is due to non-amyloidogenic processes of the amyloid-initiated cascade (Engler et al., 2006). These provocative observations suggest that amyloid therapies might be most effective in preventing AD and may not be effective in later stages of the disease (even MCI or mild AD) after substantial amyloid deposition has occurred. There is a risk that anti-amyloid therapies ineffective in patients with established disease may be abandoned, although such compounds might be effective in preventing AD if administered earlier in the clinical course.

Primary prevention studies involving normal individuals must be large due to the generally low rate of progression to MCI and AD. They will require thousands of individuals observed for several years to observe a therapeutic effect. Pharmaceutical companies are understandably reluctant to embark on such large trials in the absence of compelling evidence of efficacy. Proof of concept trials might bear on drug development decisions for such trials. Partial federal funding for such trials might also be warranted given the financial implications for Medicare and Medicaid if effective preventions for AD are not found.

Transgenic mouse models of AD are characterized primarily by Aβ deposits. In many cases prevention of Aβ deposits have been shown to be easier to accomplish than mobilization after deposition. Such observations are more relevant to AD prevention than treatment of established disease.

Summary

There are few consensus answers to the questions posed here. Clinical trials are advancing; biomarkers are being included in some trials; and alternative trial designs are being implemented. Clinical instrumentation is evolving and diagnostic standards are being reconsidered. Given the importance of identifying effective therapies for AD, collaboration of clinicians, regulatory authorities, and pharmaceutical companies is critical to the evolution of the methodologies best suited to demonstrating disease-modifying efficacy of anti-dementia therapies.

Acknowledgments

Dr Cummings is supported by an NIA Alzheimer Disease Research Center Grant (P50 AG16570), an Alzheimer Disease Research Center Grant of California, and the Sidell-Kagan Foundation.

References

Chang M, Chow SC, Pong A. Adaptive design in clinical research: Issues, opportunities, and recommendations. Journal of Biopharm Stat 2006;16:299–309.

Cummings JL. Measuring disease modification in Alzheimer's disease. CNS Spectr 2007;12:11–14.

Cummings J, Doody M, Clark C. Disease-modifying therapies for Alzheimer disease. Neurology 2007;69

Doniger G, Dwolatzky T, Zucker DM, et al. Computerized cognitive testing battery identifies mild cognitive impairment and mild dementia even in the presence of depressive symptoms. American Journal of Alzheimer's Disease 2006;21:28–36.

Dubois B, Jacova J, DeKosky J, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. Lancet Neurology 2007;6:734–746. [PubMed: 17616482]

Engler H, Forsperg A, Almkvist O, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 2006;129:2856–2866. [PubMed: 16854944]

European Medicines Agency. Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias. CPMP/EWP/553/95 Rev. London: European Medicines Agency; 2007.

Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M. A neuropsychological test battery for use in Alzheimer disease clinical trials. Arch Neurol 2007;64:1323–1329. [PubMed: 17846273]

Hendrix S, Gutin A, Zavitz K, Carron G, Laughlin M, Horton S. Modification of the staggered start and randomized withdrawal clinical trial designs: Toward a practical demonstration of disease modification in Alzheimer's disease. Alzheimer's and Dementia 2007;3:S160.

Jack, JCR.; Petersen, RC. Structural imaging approaches to Alzheimer's Disease. In: Scinto, FM.; Daffner, KR., editors. Early diagnosis of Alzheimer's disease. Totowa, NJ: Humana Press Inc; 2000.

Katz R. Biomarkers and surrogate markers: An FDA perspective. NeuroRx 2004;1:189–195. [PubMed: 15717019]

Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: A regulatory viewpoint. Stat Med 2004;23:305–314. [PubMed: 14716731]

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944. [PubMed: 6610841]

Mohs RC, Kawas C, Carrillo MC. Optimal design of clinical trials for drugs designed to slow the course of Alzheimer's disease. Alzheimer's and Dementia 2006;2:131–139.

Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992. [PubMed: 11735772]

Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. New England Journal of Medicine 2005;352:2379–2388. [PubMed: 15829527]

Rang, H. Drug discovery and development – Facts and figures. London: Churchill Livingstone Elsevier; 2006.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. American Journal of Psychiatry 1984;141:1356–1364. [PubMed: 6496779]

Sampaio C. Alzheimer disease: Disease modifying trials – Where are we? Where do we need to go? A reflective paper. Journal of Nutrition, Health & Aging 2006;10:113–115.

Sano M, Ernesto C, Thomas RG, et al. The Alzheimer's Disease Cooperative Study. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. New England Journal of Medicine 1997;336:1216–1222. [PubMed: 9110909]

Verheijen J, Huisman L, van Lent N, et al. Detection of a soluble form of BACE-1 in human cerebrospinal fluid by a sensitive activity assay. Clinical Chemistry 2006;52:1168–1174. [PubMed: 16614000]

Wang SJ, Hung HMJ, Tsong Y, Cui L. Group sequential test strategies for superiority and non-inferiority hypotheses in active controlled clinical trials. Stat Med 2001;20:903–1912.