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ALZHEIMER'S DISEASE THERAPEUTIC TRIALS: EU/US TASK FORCE REPORT ON RECRUITMENT, RETENTION, AND METHODOLOGY

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Abstract: While we may not be able to find a cure for Alzheimer's disease (AD) in the near future, several drugs presently in trials have shown promise as possible modifiers of disease progression. However, we may not be able to demonstrate efficacy due to issues of recruitment, retention, site-to-site variability, and other methodological issues. It is thus incumbent on the scientific community to find solutions to these problems, particularly as the field moves toward preventing illness or treating the disease in its prodromal stages, where these methodological issues will become even more critical. We need to better understand why participants agree or refuse to enter drug trials, and why both primary care physicians and Alzheimer's specialists agree or refuse to involve their patients. We also need to quantify the impact of requiring imaging studies, extensive questionnaires, cognitive testing, and lumbar punctures on recruitment and retention. With these concerns in mind, an international task force meeting of experts from academia and industry in the United States, European Union, and Japan in San Diego, California on November 2, 2011 to focus on recruitment, retention and other methodological issues related to clinical trials for AD. Based on the recommendations of this Task force meeting, this Perspectives article critically reflects on the most critical and timely methodological issues related to recruitment and retention in prevention and therapeutic trials in AD, which are paralleled by a paradigm shift in the diagnostic conceptualization of this disease, as reflected by recently new proposed diagnostic criteria involving preclinical stages of the disease.

Key words: Alzheimer's disease, biomarkers, neuroimaging.

Introduction

In the past few years, many drug trials have been conducted in the field of Alzheimer's disease (AD). One common denominator of virtually all finished phase III trials on disease modifying compounds in AD during the past decade has been their failure to show cognitive or clinically relevant improvement, semagacestat being the most recent example (1). While there has been much written about methodological aspects of these trials -- cognitive tests, global function, and neuropsychiatric measures, biomarkers, and imaging -- strategies for recruitment and retention have been largely neglected. In fact, there has been little research on these topics by either academia or industry over the past 20 years, despite the design and execution of many trials. Consequently, we have not improved the practical aspects of trial design and are still faced with unreasonably long periods of recruitment, too many centers but too few patients recruited by each center, and unacceptably high drop-out rates. In order to recruit for large pivotal trials today, a large number of centers may be needed from the United States, Europe, and Asia. Yet substantial variability among centers (2) results in difficulty interpreting trial results; and with the inclusion of imaging and biomarker studies in these trials, it has become more difficult to recruit and retain subjects in trials.

In 2007, an international working group proposed new research criteria for the diagnosis of AD (3), describing an AD process that begins long before the clinical stage of dementia. This notion, now widely accepted by the field, is reflected both in a 2010 revision by the working group (4) and in the new research diagnostic criteria proposed by three workgroups established by the National Institute on Aging (NIA) and the Alzheimer's Association in 2011 (5-8). This new classification scheme promises to re-shape the design of clinical trials by enabling the selection of subjects at a particular disease stage depending on the mechanism of action of the drug being tested.

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However, although greeted with enthusiasm, it should be cautioned that these are research criteria that require validation.

Identification of cognitively normal individuals on the AD spectrum who are likely to decline cognitively and transition to mild cognitive impairment (MCI) is somewhat more controversial and less clear, but certainly no less important in regard to preventing the disease at its earliest stages. Labeled "preclinical AD" in the NIA-AA model, it has been divided into three sub-stages based on biomarker findings: Stage 1 with amyloid positivity (determined with amyloid PET imaging or CSF studies) but no signs of neuronal injury and no clinical signs; Stage 2 with biomarker evidence of both amyloid and neuronal injury (positive CSF tau /p-tau, atrophy and/or hypometabolism in MRI and FDG-PET imaging, respectively) but no clinical signs; and Stage 3 with positive biomarkers and subtle cognitive deficits. In evaluating a normal population, two other stages have been proposed: Stage 0 where there is no evidence of being on the amyloid pathway and a fifth group – suspected non-amyloid pathway or SNAP -- that has cognitive signs but no AD biomarker findings. In the Mayo Clinic Study of Aging (MCSA), a population based study of cognitively normal adults, 43% were categorized as Stage 0, 16% as Stage 1, 12% as Stage 2, 3% as Stage 3, 23% as SNAP, and 4% undefined (9). In other words, this classification scheme captures the vast majority of people as they age. Interventions targeted at Stage 0 would represent true primary prevention and could target those at high risk of AD based on genetic or other risk factors but without already ongoing AD typical pathophysiology. Interventions targeted at Stages 2-4 would be called secondary prevention strategies and might involve different drugs or interventions than those used for primary prevention or to treat MCI.

Experiences from recent Alzheimer prevention trials

Several recently conducted trials were designed specifically to investigate prevention of AD, e.g., GEM (Gingko in Evaluation of Memory) (7, 9) and ADAPT (Alzheimer Disease Anti-Inflammatory Prevention Trial) (8), while other nested studies incorporated dementia prevention into existing trials. For example, memory studies were added to the Heart Protection Study, the Women's Health Initiative, and the prostate cancer prevention trial, PreAdvise (10). Sample sizes varied from about 2500 to 3000 in the primary prevention trials to over 20,000 in the Heart Protection Study (Table 1). Recruitment strategies likewise varied, and one of the lessons learned from these studies is that in order to recruit the large numbers of subjects needed, outreach must go beyond the clinic. In the United States, for example, Medicare lists or voter registration rolls can provide millions of names that can then be enriched for a particular study based on demographic characteristics such as age or gender. For trials that have biomarker requirements for entry, however, it may be more efficient to establish large registries in advance of planned prevention trials. These registries can then be mined to identify appropriate subjects for trials. For example, the Banner Alzheimer's Institute plans to establish a U.S. based "Alzheimer's Prevention Registry" comprised of people interested in learning about and possibly participating in prevention research, including a subset of as many as 50,000 individuals who undergo genetic testing to determine ApoEe4 carrier status (11).

Table 1
Recruitment Experience in AD Prevention Trials

Study	Sample size	Sites	Recruitment duration, years
GEM/ gingko biloba (12)	3069	6	1.75
ADAPT/naproxen, celecoxib (13)	2528	6	3.7
GUIDAGE/ gingko biloba (14)	2854	25	2.5
Heart Protection study/ vitamin E, C, β-carotene, simvastatin (15)	20,536	69	2.8
WHIMS/ estrogen and MPA (16)	4,532	39	2.5
SELECT/ selenium, vitamin E (17)	10,400	400	
MAPT (18)	1680	13	2.5

Recruitment may also be optimized through scientific approaches: developing comprehensive models from past prevention trials data, observational, and epidemiologic studies; simulating the effects of various recruitment strategies; and designing virtual prevention trials that factor in recruitment methods and the expected actions of a test drug.

Methodological problems, including selection bias, may help explain the disappointing results from recent clinical trials (19). Prevention studies, in particular, generally will need to encompass a representative sample of the entire population, but bias can be introduced when only a subgroup of the population takes part, e.g., those who have access to information about the study, have been invited to participate by their physician, understand the aims, agree to be followed for several years, and respond to cognitive tests. For all trials, participants also need to accept randomization, and for most trials agree to undergo lumbar puncture and imaging studies. Selection bias can thus not only limit the availability of participants but also skew results.

In order to better understand the selection bias, the Accept Study (18) was designed to analyze determinants of participation and adherence of older adults in a preventive trial. This study was an ancillary study of the MAPT trial. At baseline, when asked if they wanted to participate in MAPT, participants were also asked to complete the Accept survey and be interviewed. Results of the survey were then compared between those who agreed to participate in MAPT and those

who declined. During the follow-up phase of the study, subjects who initially accepted to participate and then decided not to continue in the entire study were invited to have an interview with a psychologist/sociologist to better understand the reasons underlying their decision to stop participating in the study.

Better education of the general public, primary care providers, and investigators about the availability of clinical trials could decrease selection bias, as could changes in the study design that decrease subject burden. Investigators also need to better explain the need for randomization to potential participants and consider innovative clinical study approaches, such as making better use of telephone, mail, and the internet to maintain contact with participants.

Recruitment and retention issues have had challenging effects on both the GuidAge and MAPT trials. In GuidAge, subjects over the age of 70 were selected based on spontaneous memory complaint to their physician. In this population, nearly 53% had CDR scores of 0.5 at baseline, but 25% of subjects dropped out, primarily in the first two years, and the remaining subjects had a low rate of decline. However, even these individuals with little exposure to the intervention have to be counted in an intention-to-treat (ITT) analysis. The primary endpoint in the study, conversion to dementia, was less than 5% over the 5-year study period. In addition, there were learning effects seen with the Free and Cued Selective Reminding Test (FCSRT), which made it difficult to detect a preventive effect. Family physicians were used successfully in this study to assess compliance, deliver medications, and assess safety; and compliance was high among those who stayed in the study.

MAPT enrolled 1680 pre-frail subjects with slow walking speed, subjective memory complaint to their primary care provider, and limitation on one instrumental activity of daily living (IADL). Subjects were recruited through a network of memory clinics in small cities in southern France. Frailty appears to be a good selection criterion for subjects close to conversion, since studies have shown that frail and pre-frail subjects are more likely to have cognitive decline. Using small memory clinics associated with a larger center also proved to be an efficient approach for recruiting and maintaining patients. Interestingly, a subset of subjects enrolled in MAPT who underwent PET imaging showed bilateral temporal hypometabolism by FDG-PET and the presence of amyloid deposits by florbetapir amyloid imaging in 45% of subjects (n=130). These observations suggest that in future prevention trials, inclusion criteria can include: age over 70, subjective memory complaint, pre-frailty, and amyloid PET positivity with absent objective memory deficits or clinical symptoms at baseline. Subjects with MMSE scores of 30 should probably be excluded, and a subset of subjects should undergo MRI and amyloid PET imaging.

The Alzheimer's Prevention Initiative (API) is an international collaborative project developed by the Banner Alzheimer's Institute in Phoenix, Arizona. The API portfolio includes two sets of trials of one or more amyloid modifying therapies in individuals with pre-symptomatic AD. One set of trials will be conducted in partnership with Francisco Lopera and colleagues among members of an extended family in Antioquia, Colombia, roughly a third of whom carry the autosomal dominant E280A PSEN1 mutation, which causes early onset AD (EOAD), as well as affected families in the United States. The second set of trials will be conducted in persons who are carriers of the ApoEe4 allele, which puts them at high risk of developing late onset AD (LOAD). Registries are being established for both of these studies. The goal is to register 3,000 individuals in Colombia and 250,000 individuals in North America, including 50,000 over the age of 50 with ApoE genotypes for the LOAD study. At the time of the Task Force meeting, about 1250 individuals in Colombia had been genotyped, identifying 376 carriers of whom 267 are cognitively normal. The infrastructure has been established for MRI, PET, and fluid biomarker studies and preliminary data have been collected in preparation for the first clinical trial. Since the current community standard in Colombia and most of North America is non-disclosure, carriers will be randomized to receive treatment or placebo; non-carriers will receive only placebo. If disclosure standards change, API will modify its plan. The specific agent to be tested in the first trial has not yet been publicly announced. The investigators stressed the fact that the studies proposed require full funding and vetting by key stakeholders including ethical and regulatory authorities.

The Dominantly Inherited Alzheimer's Network (DIAN) is a longitudinal biomarker study of adult children of parents with dominantly inherited AD-causing mutations at 11 sites in the United States, the United Kingdom, and Australia. The goals are to determine when AD-related pathobiology begins, and at what sequence and rate it changes in pre-symptomatic mutation carriers in relation to parental age of onset of dementia; and to compare the clinical and pathological phenotypes in dominantly inherited EOAD versus LOAD. The study was funded to enroll 400 participants. Halfway through the funding period, more than 200 individuals have been enrolled and completed a battery of assessments including the Clinical Dementia Rating scale, an extensive psychometric battery, the International Personality Item Pool, blood and CSF studies, MRI, FDG-PET, and PET-PIB. Compliance has been very high at more than 90% for study assessments, although slightly lower for lumbar punctures at approximately 75%. Although DIAN is not funded to do clinical trials, a therapeutic trials unit has been established that will use the DIAN cohort. The DIAN Therapeutic Trials Unit will conduct studies with three agents with different mechanisms of action , and if any of these drugs show a biomarker effect, a clinical study will be initiated.

Industry recruitment experience

The Avagacestat (BMS-708163) study (NCT00890890) was the first randomized controlled trial to prospectively recruit and finish enrollment of patients with prodromal AD. Recruitment

was done at 72 sites over approximately 24 months. Patients were evaluated on clinical criteria, and then those deemed likely to have prodromal AD underwent LPs for biomarker studies. There was a high screen failure rate: only about 20% of those screened qualified for the study. These findings show that while a phase 2 study is possible using this approach, it might be challenging to move to phase 3. As part of the study, florbetapir amyloid imaging was done in 77 subjects, and these studies showed excellent concordance with pathological CSF criteria, suggesting that amyloid imaging and CSF biomarkers reflect the same underlying pathology. Since amyloid imaging may be more acceptable to both patients and investigators, use of amyloid imaging might increase the flow of patients to studies.

Bapineuzumab, a monoclonal immunotherapeutic, is now in two separate phase 3 studies, one in ApoEe4 carriers and one in non-carriers. These trials follow two phase 2 studies, which showed different responses among these two groups and that the occurrence of amyloid-related imaging abnormalities (ARIA) was increased in ApoEe4 carriers (20). This has complicated recruitment, since carriers are randomized to only one dose, but non-carriers are randomized to two doses. Thus, more non-carriers are needed than carriers even though carriers tend to volunteer more frequently than non-carriers for clinical trials. As result, non-carrier recruitment has taken longer and there have been more screen failures (i.e., carriers turned away because that arm has been fulfilled). Other recruitment challenges have arisen from the fact that this is an international trial, and countries vary in terms of their recruitment capability. Instruments and scales must be adapted for different languages and cultures, and different countries have different reporting requirements. Thus, when international trials are planned, it is important to engage investigators and health and regulatory authorities early in the process.

Dimebon, an antihistamine used in Russia since 1983, was shown in the 1990s to have a novel neurochemical activity, presumably through the enhancement of mitochondrial function. After promising trials in Russia, the drug was tested in a six-month randomized placebo-controlled monotherapy trial (CONNECTION) at 70 centers in the United States, Europe, Chile, and Russia. During the 14 month enrollment phase, it became clear that at academic centers, it was difficult to recruit subjects who were not already taking an AD medication, so the sponsor relied on recruitment at non-academic centers. Retention was excellent but the trial failed to show efficacy at either of two doses. However, there is some concern that the six month trial was too short to show efficacy, particularly when, as in this study, the population was not enriched for those likely to decline over six months. This study was followed by a 12-month add-on study (CONCERT) that enrolled subjects already taking donepezil or memantine. This study is currently ongoing. Add-on studies have both advantages and disadvantages. On the one hand, patients who have been treated with AD drugs may be more likely to have the disease than those who are untreated and recruited through advertising. On the other hand, treatment with a drug such as donepezil may itself slow decline on the ADAS-Cog and ADCS-ADL (the primary endpoints), masking any effect of the drug being tested. Recruitment may however be negatively affected by non-add-on approaches, since AD patients are less likely to participate in trials which require subjects to deliberately decline approved AD drug treatment. CONCERT has had a similar enrollment rate as CONNECTION, but more academic centers contributing to the study compared to non-academic centers. Early discontinuation rates have been low overall, but somewhat higher in non-academic than academic centers. Practices that were initiated to increase retention included maintaining active and ongoing communication with site staff, following up with each patient who discontinued early, better educating site staff, and assisting patients with transportation to the center.

Differences in recruitment were also seen among various countries and between academic and non-academic sites in the semagacestat and solanezumab trials. The contract and IRB approval process was delayed in many countries, although some of these countries made up for that delay by speeding up recruitment. Contracts also took longer at academic vs. non-academic sites but recruitment rates were not all that different.

Retention takes on increasing importance for longer studies. In the 78-week phase 2 study of ELND005 (scyllo-inositol), for example, 39% of subjects dropped out before the end of the trial. Compared to those who completed the trial, dropouts tended to be older and had more severe AD, higher Neuropsychiatric Inventory (NPI) scores, and more white matter disease. Retention strategies targeted at these subjects may decrease this unacceptably high attrition rate.

Impact of imaging and biomarkers on recruitment and maintenance

The use of biomarkers has had a substantial impact on both recruitment and retention worldwide, primarily due to increased subject burden and the availability and cost of performing biomarker studies. There is also significant variability among countries with regard to cost and availability, as well as with trial experience, center and investigator quality, and IRB processes. As trials get more complicated, this diversity hampers uniform trial management and application of methodologies. Mandatory inclusion of biomarker and genetic testing could greatly improve the selection and stratification of appropriate subjects for trials, particularly subjects in the earliest stages of disease; however, unresolved issues regarding reliability, standardization, and validation raise questions about the feasibility of this approach at the present time (21). Moreover, biomarker studies increase the cost of trials, although these costs are offset by more efficient trials in more homogeneous populations. Using data from 19 studies to simulate a trial, using CSF biomarkers to select subjects

reduced sample size by 67% and trials costs by 60% compared to a trial with unselected subjects with MCI (22).

For selection of subjects in phase 3 trials, amyloid PET imaging with an amyloid imaging agent is perhaps the most useful since it reflects the level of amyloid pathology in the brain and is non invasive. Moreover, PET imaging is widely available in many areas because of its use in cancer treatment, and regulatory agencies appear nearly ready to accept florbetapir as a measure of brain amyloid, which should lead to increased use. Major problems with PET are its high cost, reliability of production of the ligand, and radiation exposure. In addition, variability among centers may be introduced based on the use of and experience with different image analysis modalities.

CSF Aβ1-42 also appears to reflect brain amyloid burden, and thus could be used as an alternative to amyloid PET imaging for inclusion purposes, particularly if standardization issues and patient acceptance for lumbar punctures (LPs) can be managed. Other biomarker tests such as CSF tau, FDG-PET, and MRI may also be useful for subject selection particularly when non-amyloid therapies are being tested; however these tests are likely more useful as outcome measures.

How acceptable are these tests to participants? Multiple imaging sessions (e.g. after each infusion) may increase attrition since it is a burden on patients and caregivers. Experience from the Dominantly Inherited Alzheimer Network (DIAN) suggests that challenging cognitive testing may be considered an even greater burden than LP or imaging. Genetic testing requires experience and training to present to families. Moreover, measures to ensure privacy are necessary. CSF sampling suffers from a bad reputation in the public as well as among some physicians and even poses important ethical considerations (23); and in some countries (e.g., USA), requiring a lumbar puncture has had an adverse effect on recruitment. The negative public image, however, is in strong opposition to a number of studies showing that in a memory clinic setting, the frequency of post lumbar puncture headache is statistically marginal while neurological or other complications are almost absent. This important information needs to be actively presented to patients, their proxies and general practitioners, and may help to reduce reservations and increase acceptance and adherence.

Similar to CSF biomarkers (24), neuroimaging provides important potential stage-dependent diagnostic and outcome markers in AD trials (25, 26). However, long scanning times, e.g. during extended MRI or PET scanning sessions, may also contribute to reduced adherence. Elderly subjects with preexisting musculoskeletal issues are prone to complain about neck and lower back pain while lying still during imaging sessions lasting longer than 20-30 minutes. MRI protocols involving more than just safety MRI, e.g. protocols consisting of additional functional MRI and/or DTI measurements exceeding 30-60 minutes of total scan time should thus be accompanied by specific measures in order to reduce positional problems: the duration of MR imaging sessions should be kept to a minimum and include only very important imaging outcome parameters. Very long imaging sessions should be divided into shorter sessions, separated by short breaks allowing the patient to refresh, relax, stretch or visit the restroom.

The FDA has suggested that clinical trials using anti-amyloid therapies screen and monitor patients for amyloid related imaging abnormalities (ARIA) resulting from edema (ARIA-E) or microhemorrhages (ARIA-H) (27). The FDA criteria pertain to AD trials longer than three months in duration with compounds that target Aβ in the brain. Patients must have an MRI at baseline, and will be excluded if there is evidence of more than four cerebral microhemorrhages, a single area of superficial siderosis, or evidence of a prior macrohemorrhage. The microhemorrhage cutoff is relatively generous, excluding a low percentage of patients. There are additional recommendations regarding the minimum frequency of MRI monitoring and discontinuation criteria. This stems from the need to monitor patients for ARIA as a treatment side effect. Screening for ARIA will have a negative impact on patient recruitment since some candidates with abnormal findings on baseline examinations will be excluded from participation. However, patient retention may be enhanced if subjects with clear scans at baseline are less likely to experience adverse events. Additional layers of scrutiny are also being added in some countries, which may further impact recruitment and retention.

Methodological and statistical approaches for dealing with missing data and the use of adaptive designs

Methodological issues also play important roles in the likely success of clinical trials, and may have been responsible for some of the recent failures. Assessing the efficacy of an intervention with cognitive or functional measurements repeated periodically over a long period of time requires the selection of a statistical model that can adapt to missing data and highly variable clinical assessments. Biostatisticians used data from five ADCS studies to compare four types of mixed-effects models (28). This meta-analysis confirmed that the choice of model yields noticeable differences in point estimates and their confidence intervals. While categorical time models resulted in tighter confidence intervals, continuous time models with fewer parameters were favored by Akaike information criterion (AIC), which estimates the predictive characteristics of a model. None of the models showed a consistent bias, and more simulations are needed to assess whether one model is more honest and robust than the others.

The problem of missing data has been addressed by both the European Medicines Agency (EMA) (29) and the National Research Council (30). While these reports concluded that there are statistical techniques to deal with missing data, the best solution is to avoid dropouts. Trial designs should thus focus on

maximizing the number of participants maintained throughout the trial. Moreover, statistical methods should only be used when the assumptions underlying them are scientifically justified.

More efficient clinical trials may also require adaptive designs, which are loosely grouped as frequentist or Bayesian. The FDA issued a draft guidance in February 2010 that defined adaptive designs as those that are "prospectively planned for modification of one or more specified aspects of the study design and hypothesis based on analysis of (usually interim) data." PhRMA also has weighed in on the adaptive design issue, emphasizing that modifications in trial design based on accumulating data must not undermine the validity or integrity of the trial. Thus, if a study has remained unequivocally blinded, it may be reasonable to modify the trial after an interim analysis of data such as aggregate event rates, variance of response measures, discontinuation rates, or baseline characteristics. Some of the more familiar adaptions include repowering based on aggregate data, modifying eligibility criteria, and including group sequential methods or futility analyses. Less familiar methods include adapting randomization or sample size based on interim effect size estimates, or even adapting the primary outcome.

A well-documented use of Bayesian adaptive design methodology is being used in the I-SPY 2 Breast Cancer Clinical trial, which uses multiple investigational drugs thought to target different biological pathways based on an analysis of the individual's tumor. Investigators hope that by using an adaptive design, they will be able to run smaller and less expensive trials of various drugs personalized to different tumor variants.

Discussion

While there was widespread agreement that identification of amyloid pathology as a prerequisite for prodromal AD trials is desirable, many questions remained about the practicality of such a requirement. One reason for the lack of a clear consensus is that the recently proposed diagnostic AD criteria by the NIA-AA did not weigh a positive amyloid signal higher than other biomarkers, and the best inclusion marker for a given trial depends on the mechanism of action of the drug. Task Force members did agree, however, that MRI evidence of hippocampal atrophy is not specific enough to be used as an inclusion criterion.

Whether trials should only enroll untreated subjects was another unresolved question. Since so many people with memory complaints are treated with cholinesterase inhibitors and/or memantine, it may be impractical to exclude them from trials. Moreover, there is evidence that patients already on symptomatic therapy deteriorate faster in clinical trials (31). In addition, there could be synergistic drug interactions that further confound the interpretation of results.

In addition to sharing strategies that have been implemented to increase the efficiency of clinical trials, the Task Force identified several issues related to clinical trials recruitment, retention, and methodology that require further attention and research in order to maximize the likelihood of success in preventing or treating AD. These include research to:

- Better understand why patients and physicians choose to participate or not participate in clinical trials
- Identify and implement strategies to address cultural and psychological factors that reduce participation in trials
- Determine the impact of requiring imaging studies and lumbar punctures as a condition of participation in clinical trials
- Develop strategies to decrease variability among centers
- Adapt existing clinical and research networks to enable recruitment of large numbers of patients with access to imaging and biomarker studies
- Model the dropout process to identify strategies to reduce dropouts

AD is a common disease among the elderly, but in order to increase recruitment, we need to adapt our clinical research facilities, building Alzheimer's disease clinical research centers with well-organized local networks to give access to trials to the older patients living in the community. Typically, research centers with the facilities for imaging and biomarker studies lack sufficient access to patients, while clinical facilities that may have many eligible patients often have poor access to these important research tools. A trial might involve only about 20 centers, with each center recruiting 20 patients for a 400 subject trial; however, this would require a better use of available resources. Patient registries are also useful but not easy to build in practice. Recommendations will be useful to build such registers and deal with ethical issues. Since the typical AD patient is old, isolated, with memory impairment, with reluctant relatives and health care professionals, it is time now to develop organizational research on Alzheimer's recruitment issues, retention and other methodological issues if we are to achieve success (32).

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References

1. Schor NF (2011) What the halted phase III gamma-secretase inhibitor trial may (or may not) be telling us. Ann Neurol 69: 237–239.
2. Mattsson N, Andreasson U, Persson S, Arai H, Batish SD, Bernardini S, Bocchio-Chiavetto L, Blankenstein MA, Carrillo MC, Chalbot S, et al (2011) The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement 7: 386–395.
3. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, et al (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 6: 734–746.
4. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, et al (2010) Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9: 1118–1127.
5. Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7: 270–279.
6. Jack CR, Jr, Albert M, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH (2011) Introduction to revised criteria for the diagnosis of Alzheimer's disease: National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 7: 257–262.
7. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, et al (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 7: 263–269.
8. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, et al (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 7: 280–292.
9. Kantarci K, Lowe V, Przybelski SA, Weigand SD, Senjem ML, Ivnik RJ, Preboske GM, Roberts R, Geda YE, Boeve BF, et al (2012) APOE modifies the association between Abeta load and cognition in cognitively normal older adults. Neurology 78: 232–240.
10. Schneider LS: Recruitment methods for United States Alzheimer disease prevention trials. J Nutr Health Aging. In Press (2012).
11. Sabbagh MN, Tariot PN (2009) Commentary on "a roadmap for the prevention of dementia II. Leon Thal Symposium 2008." A national registry to identify a cohort for Alzheimer's disease prevention studies. Alzheimers Dement 5: 128–129.
12. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM, DeKosky ST (2009) Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA 302: 2663–2670.
13. Meinert CL, McCaffrey LD, Breitner JC (2009) Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. Alzheimers Dement 5: 93–104
14. Vellas B, Andrieu S, Ousset PJ, Ouzid M, Mathiex-Fortunet H (2006) The GuidAge study: methodological issues. A 5-year double-blind randomized trial of the efficacy of EGb 761 for prevention of Alzheimer disease in patients over 70 with a memory complaint. Neurology 67: S6–S11.
15. Heart Protection Study Collaborative Group (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo controlled trial. The Lancet 360: 7–22.
16. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN, 3rd, Assaf AR, Jackson RD, et al (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289: 2651–2662.
17. Kryscio RJ, Mendiondo MS, Schmitt FA, Markesbery WR (2004) Designing a large prevention trial: statistical issues. Stat Med 23: 285–296.
18. Andrieu S, Aboderin I, Baeyens JP, Beard J, Benetos A, Berrut G, Brainin M, Cha HB, Chen LK, Du P, et al (2011) IAGG workshop: health promotion program on prevention of late onset dementia. J Nutr Health Aging 15: 562–575.
19. Coley N, Andrieu S, Gardette V, Gillette-Guyonnet S, Sanz C, Vellas B, Grand A (2008) Dementia prevention: methodological explanations for inconsistent results. Epidemiol Rev 30: 35–66.
20. Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, et al (2009) A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 73: 2061–2070.
21. Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde AL, Jessen F, Hoessler YC, et al (2010) Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov 9: 560–574.
22. van Rossum IA, Vos S, Handels R, Visser PJ (2010) Biomarkers as predictors for conversion from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. J Alzheimers Dis 20: 881–891.
23. Prvulovic D, Hampel H (2011) Ethical considerations of biomarker use in neurodegenerative diseases-A case study of Alzheimer's disease. Prog Neurobiol 95: 517–519.
24. Blennow K, Hampel H, Weiner M, Zetterberg H (2010) Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol 6: 131–144.
25. Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H (2011) Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. Trends Neurosci 34: 430–442.
26. Hampel H, Wilcock G, Andrieu S, Aisen P, Blennow K, Broich K, Carrillo M, Fox NC, Frisoni GB, Isaac M, et al (2011) Biomarkers for Alzheimer's disease therapeutic trials. Prog Neurobiol 95: 579–593.
27. Sperling RA, Jack CR, Jr., Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, et al (2011) Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement 7: 367–385.
28. Donohue MC, Aisen P (2012) Profile models versus slope models for assessing longitudinal change in Alzheimer's disease clinical trials. J Nutr Health Aging. In Press.
29. European Medicines Agency CHMP (2010) Guidelines on Missing Data in Confirmatory Clinical Trials. London, United Kingdom.
30. National Research Council Panel on Handling Missing Data in Clinical Trials (2010) The Prevention and Treatment of Missing Data in Clinical Trials. National Academies Press, Washington.
31. Schneider LS, Insel PS, Weiner MW (2011) Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol 68: 58–66.
32. Hampel H, Prvulovic D (2012) Are biomarkers harmful to recruitment and retention in Alzheimer's disease clinical trials? An international perspective. J Nutr Health Aging. In Press.